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CAPILLARY RESISTANCE STUDIES

Part I: The Newborn Infant

BY

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AND

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VISCERAL and intracranial haemorrhages are generally accepted as frequent findings in stillbirths and neonatal deaths. The importance of trauma and anoxia particularly in premature babies is apparent but the significance of defects in the clotting mechanism and of the fragility of the capillary bed are still subject to discussion. Earlier pathologists (Spencer, 1891) believed "asphyxia" an adequate explanation for visceral and intracranial haemorrhage but Ylppö (1924) stressed the role of prematurity and suggested that capillary weakness was a major factor favouring the occurrence of haemorrhage. It appears established that prematurity is associated with outstanding capillary fragility and that this can be reliably estimated by a variety of techniques (Ylppö, 1924; Lindquist, 1937; Minkowski and Venes, 1948).

Capillary strength is known to be affected by certain vitamins (Munro *et al.*, 1947) and it has been established that seasonal variations occur in the adult. Kerpel-Fronius *et al.* (1948) have demonstrated a similar seasonal trend in children and suggest that this parallels the observed seasonal trend in intracranial haemorrhage in the newborn in Hungary.

The present enquiry was planned to investigate seasonal trends in capillary resistance in the newborn and to relate these to the observed incidence of intracranial haemorrhage. At the same time since Vitamin P is claimed to influence resistance in the newborn (Kerpel-Fronius *et al.*, 1948; Minkowski and Venes, 1948) a comparison was made between babies born of mothers given this vitamin antenatally and a control group.

REVIEW OF METHODS

A modification of the Dalldorf (1933) negative pressure test as described below was employed because it presented the least difficulty in standardization, particularly when working with infants, and thereby allowed of a greater accuracy in the results. The apparatus used was a slight modification of that described by Scarborough (1941). Fig. 1 shows a hand-suction pump (A) which is used to evacuate a vacuum reservoir (B). (C) is a fine adjustment valve by which the mercury can be sucked into the manometer (D) from the mercury reservoir (E). The mercury can be drawn up to any given level and steadily maintained to an accuracy of plus or minus 10 mm. by means of the valve. Distal to the valve there is a side arm to which the suction cups (F) are attached. When the cup is applied to the skin, the pressure within it is, therefore, the same as that indicated by the manometer. Although the time of exposure of the skin to the negative pressure is usually stated, it has not been made clear by some authors

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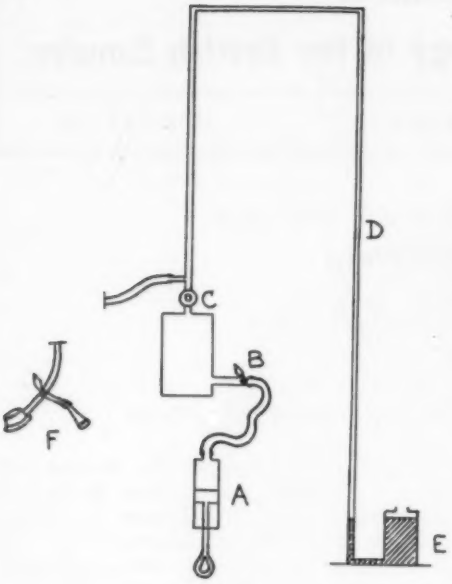

FIG. 1

whether the 30 or 60 seconds exposure includes or excludes the time taken for the apparatus to attain that pressure. Rough laboratory tests showed that the time taken for a water tap apparatus as used by Ylppö (1924) to reach a given pressure was much longer than the mercury manometer method used in the present experiments, and this author states the necessity of reaching a given pressure within a definite time.

Area tested. Results can be compared only if the tests are made on the same area of the body. Bell *et al.* (1940, 1942) found a low correlation between the results on various parts of the arm, as did Lindquist (1935, 1937) on the leg, trunk and limbs. The infra-clavicular area has been used (Bayer, 1930) and the sub-scapular area of the back (Bayer, 1930; Ylppö, 1924; Minkowski and Venes, 1948), but in the infant, no standard area has yet been established. It was suggested by Gothlin (1937) and Roberts, Blair and Bailey (1937) that greater accuracy could be obtained by testing both sides of the body and calculating an average.

Size of Suction Cup. Cups varying from 3·5 cm. (da Silva-Mello, 1929) to 0·5 cm. (Abt, Farmer and Epstein, 1936) in diameter have been used and such variation is held not to influence the results. Frontali (1922), Weimer (1931), and Lindquist (1937) used 2 cm. and 1 cm. diameter cups and found no great difference in the results but did report more petechiae at any given pressure with the larger cup. A small experiment was, therefore, devised whereby the relationship between two cups could be ascertained. These had inner diameters of 2 cm. and 1 cm. respectively and 42 infants were tested with both in the manner described above; 67 estimations were made in all. The tests were performed as close together as possible on the back and they were completed within about 5 minutes of one another (Fig. 2).

It can be seen (Fig. 2) that a much higher pressure was required to obtain a positive result with the smaller cup.

Many of the tests with the small cup read above 500 mm.Hg (the maximum accurate reading of the apparatus) and seemed to produce discomfort.

As there appeared to be a close correlation between the cups and as the small cup necessitates pressures high enough to produce discomfort, there seemed little to be gained by the use of the small one. It can be used, however, in the case of premature infants where the surface area available for testing is small, and where the critical level, even with the small cup, is well below

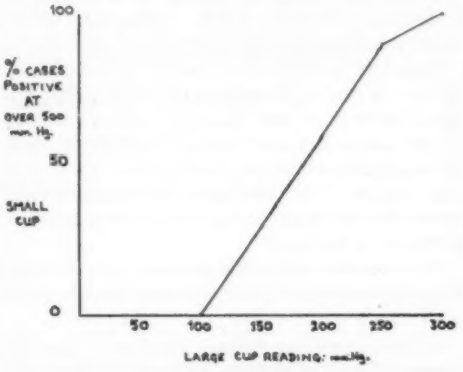

FIG. 2

500 mm.Hg, i.e. below the levels apparently causing pain.

The large cup was, therefore, adopted for all further experiments on mature infants.

Critical Petechial Pressure. The strength of a capillary is estimated by the production of petechiae and many authors define their own criteria of positivity. This information is obviously of importance if the results (in terms of numbers of cases positive) of two different series are to be compared. The "critical petechial pressure" was estimated by raising or lowering the negative force by 50 mm.Hg until a pressure which produced between 1 and 9 petechiae was reached. After an initial survey of about 50 cases, it was decided that the pressure producing 1 petechia only could be regarded as "critical", but a confirmatory negative result was always obtained with a pressure of 50 mm.Hg lower. The negative pressure in all experiments was applied for 60 seconds (excluding the few seconds taken to reach that level) and the source of light was a 250-watt "photo flood" electric bulb. The importance of standardized lighting has been stressed by Bell, Lazarus and Munro (1940) and Gothlin (1937), the latter using a hand lens to examine the test area.

Bruising and Oedema. A bluish discoloration resembling a bruise is mentioned by Bayer (1930). Unlike Minkowski (1951) he found no relation between this finding and the infant's weight. He also reported a deeper bruise on a single occasion and free intra-cutaneous bleeding, bruising and oedema have been reported by several workers (Ylppö, 1924; Abt *et al.*, 1936; Lindquist, 1937; Maloney, 1943). Lindquist (1937) considered the production of oedema important only in so far as it restricted the circulation and thus reduced petechial formation. The relationship between the production of bruising and oedema and petechial formation is shown in Fig. 3.

The tests were divided into four groups, those showing no petechiae, those showing 1 to 5, 5 to 10, and over 10 petechiae respectively, and the presence or absence of bruising and oedema was tabulated for each group.

Inspection of Fig. 3 demonstrates an increase of bruising and/or oedema as the number of petechiae increases. There was a steady rise in the incidence of bruising alone from 4 per cent in the cases showing no petechiae to 30 per cent in those showing over 10, and an inverse trend is observed in those cases free from both oedema and bruising.

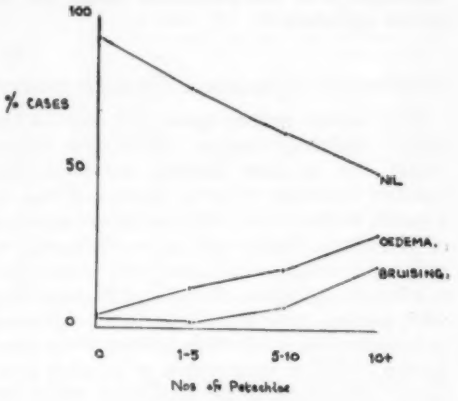

FIG. 3

Co-operation of the Infant. A further source of error, not mentioned by previous authors, was noted during the present investigation. It became obvious that a greater number of petechiae was produced at any given pressure when the infant was restless or crying than when it was lying quietly. For this reason, certain tests had to be abandoned.

Time of Testing. There appears to be some change in capillary resistance within the course of a day (Munro *et al.*, 1947) and this may be related in some way to meals. It is impracticable to test all babies at the same time after feeds when large numbers of infants are being tested. Likewise, since the infants were born at all times of day or night, the first infant tests had no fixed relation to the time of day or to meal-times.

The cup was held firmly against the chest wall in order to give as airtight a union as possible and it was seldom necessary to press very hard. The skin was examined for petechiae prior to testing and that number subtracted from the final results. If oedema was produced, it was allowed to disperse before the final petechial count was taken and a note was made of the presence or absence of a bluish discoloration

over the whole cup site. The area tested was examined by a hand lens unless frank purpura was produced.

The infants were mature and free at the first testing from manifest infection or congenital abnormality. A few premature babies are reported separately.

Investigation of Seasonal Trends in Infants

Most recent writers agree with two of the earlier workers, Gothlin (1931) and Gedda (1931), that in older children and adults the capillary resistance is low in spring and high in autumn. Roberts *et al.* (1937) in the examination of 85 children found April to be the month in which the resistance was lowest and August that in which it was highest. Brewer (1938) examining adult women, however, found a lower resistance in autumn than in the other seasons of the year. Brown (1947) on examination of 60 cases gives winter and spring as the seasons in which the fragility was most marked. Munro *et al.* (1947) state that spring and summer show the lower resistance and winter and autumn show the higher. Kerpel-Fronius *et al.* (1948) on examination of 233 children found resistance greater in the second six months of the year, March and April being the months showing the lowest figures.

There is evidence that the incidence of stillborn infants shows slight seasonal variation (Sutherland, 1949; Fig. 1). Waddell and Lawson (1940) attempted to show a seasonal variation in neonatal deaths from intracranial haemorrhage, and suggested that hypoprothrombinaemia played a contributory part in the production of the haemorrhage. Their figures for the first 2 days of life, however, showed no such tendency, and the claim that Vitamin K might reduce deaths from intracranial haemorrhage is doubted (Potter, 1952). Dam *et al.* (1952) have published figures showing a seasonal variation in deaths from intracranial haemorrhage in premature infants. They were unable to detect any seasonal trend in the prothrombin level at birth, though a marked trend was apparent a few days later.

Bayer (1931) examined 13 cases of cephalhaematoma and found the capillary resistance lowered in 8 of them. Hartley and Burnett (1944), on the other hand, do not mention capillary tests in their study of this condition and think that cephalhaematomata occur in skull bones showing irregular ossification and that hypoprothrombinaemia may be an additional factor. Potter (1952), however, states that the underlying bone is "almost never abnormal".

Kerpel-Fronius *et al.* (1948) reported a close seasonal relationship between capillary resistance of young children and the incidence of certain haemorrhagic manifestations in the newborn. March and April were found to be the months in which fragility was greatest.

Investigations were, therefore, planned to see if there was a seasonal variation in the capillary resistance, not of the older infants as shown by Kerpel-Fronius *et al.* (1948), but of the newborn, and also to find out if there was a parallel seasonal incidence of neonatal intracranial haemorrhage in Edinburgh. The city is stated advisedly as climatic (Brown and Watson, 1941) and dietetic (see below) conditions vary markedly from place to place and these may influence capillary fragility.

The investigations were performed over an 18-months period, October, 1949, to March, 1951, inclusive, during which time 1,735 estimations of capillary resistance were made during 709 examinations of 518 newborn babies. The results obtained during the early months were discarded owing to possible inaccuracies while the technique was being perfected; thus 622 test results were used in the final analysis. Kerpel-Fronius *et al.* (1948) considered pressure below 150 mm.Hg to be low, but it became obvious that, when testing the normal newborn infant, figures of 50 mm.Hg and 100 mm.Hg were often obtained within 24 hours of birth. The apparatus was not accurate below 50 mm.Hg and, therefore, no absolute figure could be quoted as being low. Experience showed that the best method of examining the results was to divide the cases into those positive (i.e. showing petechiae as described above) at 100 mm.Hg or less, and those positive at 150 mm.Hg or more. The 622 test results are reproduced in Table I and it can be seen from these that there is no marked seasonal change in the capillary resistance in any of the age groups into which the cases have been divided.

TABLE I

Seasonal and Age Analysis—622 Tests

Month	Under 24 hours				24 hours to 4 days				5 days and over			
	+ve at 100—		+ve at 150+		+ve at 100—		+ve at 150+		+ve at 100—		+ve at 150+	
	No.	per cent	No.	per cent	No.	per cent	No.	per cent	No.	per cent	No.	per cent
January	8	80	2	20	18	34	35	66	0	—	15	100
February	9	90	1	10	33	63	19	37	4	36	9	64
March	6	67	3	33	19	50	19	50	6	33	12	67
April	12	92	1	8	16	50	16	50	3	33	6	67
May	21	72	8	28	15	43	20	57	6	23	20	77
June	23	82	5	18	5	26	14	74	2	15	11	85
July	9	69	4	31	13	54	11	46	0	—	1	100
August	—	—	—	—	—	—	—	—	—	—	—	—
September	22	88	3	12	7	54	6	46	—	—	—	—
October	28	87	4	13	24	55	20	45	—	—	—	—
November	3	100	0	—	1	25	3	75	1	33	2	67
December	14	100	0	—	14	64	8	36	1	50	1	50
Totals	155	83	31	17	165	49	171	51	23	23	77	77

Examination of the results in two monthly groups as done by Kerpel-Fronius *et al.* (1948) shows an apparent rise in resistance in spring and summer, in the cases in which intracranial haemorrhage is most likely to be manifest—namely, those under 24 hours old.

The graph of the cases tested between the ages of 1 and 4 days of age does not show an identical curve, but again the tendency is for the resistance to be highest in the summer (Fig. 4). Statistical analysis of Table II failed to show any significant seasonal variation and no trend could be detected by any re-arrangement of the monthly grouping. It would be unwise to draw any conclusions from this investigation, except that the newborn infant does not appear to have the same seasonal trends in capillary resistance as do older children or adults. Seasonal trends in capillary function appear then to be at the most only a minor contributory factor in the production of seasonal variations in intracranial haemorrhage in the newborn.

TABLE II

Percentage of cases positive at 150 mm.Hg or more

	24 hours	1 to 4 days	5+ days
January, February	15	52	82
March, April	21	50	67
May, June	23	66	81
July, August	31	46	—
September, October	13	45	—
November, December	—	51	58

Seasonal Variation in Fatal and Non-fatal Haemorrhage in Foetus and newborn

The seasonal incidence of cephalhaematoma over a 2-year period was obtained from the infant case records of the Simpson Maternity Pavilion, Edinburgh. Although there is apparently a slight increase in the incidence in the months May and June (Fig. 4), the trend is not very marked and evidently does not confirm the report of Kerpel-Fronius *et al.* (1948).

An analysis of post-mortem evidence of certain intracranial haemorrhages and pulmonary haemorrhage is presented in Table III.

Only the stillbirths with subarachnoid and intraventricular haemorrhage show a significant seasonal variation with many more cases in the second quarter than at other times. This group, however, comprises only 9 per cent (63) of the total of 665 cases listed. It can be said, therefore, that there is no significant seasonal variation in

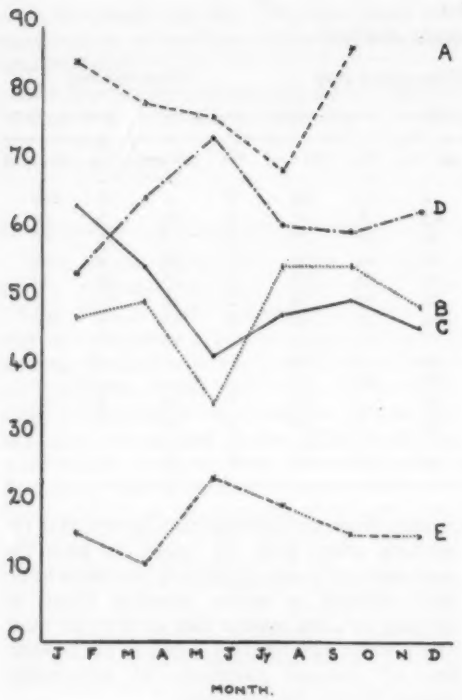

FIG. 4

Seasonal variation in capillary resistance compared with post-mortem statistics for intracranial haemorrhage in the newborn.

A = Age 0-1 days. Per cent of babies with a capillary resistance of 100 mm.Hg or less ×— — —×

B = Age 2-4 days. Per cent of babies with a capillary resistance of 100 mm.Hg or less |·····|

C = Bimonthly Totals—Subdural haemorrhage, 1941-48. •————•

D = Bimonthly Totals—Subarachnoid and/or intraventricular haemorrhage, 1941-48 o— · —· o

E = Bimonthly Totals—Cephalhaematoma, 1945-48. ×— — — — —×

intracranial haemorrhage as a whole, such as is described by Kerpel-Fronius *et al.* (1948). In view of the findings in the previous section, it seems unlikely that seasonal changes in capillary resistance have any close relationship with intracranial haemorrhage in the newborn. Even if the trends were fully significant, the months during which the resistance is low (the first and fourth quarter) do not correspond with those in which

TABLE III

Seasonal incidence of Intracranial and Pulmonary Centre Haemorrhage at autopsy

	Jan. to Mar. 1	April to June 2	July to Sept. 3	Oct. to Dec. 4	Total
1941-48 inclusive:					
Live births:					
S.D.	38	28	31	33	130
S.A.+I.V. ..	62	81	86	77	306
Stillbirths:					
S.D.	49	36	39	42	166
S.A.+I.V. ..	19	30	6	8	63
3 year Pulm. Haem. period 1946-48 ..	32	39	27	22	120

NOTE: S.A.+I.V. stillbirths = 63
other I.C.H. = 602
that is, in 9 per cent of total I.C.H. a seasonal variation can be shown.

Key: S.D. = sub-dural
S.A. = sub-arachnoid
I.V. = intraventricular

the intracranial haemorrhage is most evident (the second quarter). The seasonal trend in capillary resistance is compared with the seasonal incidence of intracranial and intrapulmonary haemorrhage, of stillbirths and of cephalhaematoma in Fig. 4.

It appears possible that pulmonary haemorrhage may show a seasonal trend unrelated to the incidence of prematurity or infections. It is impossible, however, with the figures available to make a strict comparison with the capillary resistance figures.

One final observation should be made on studying Fig. 4. Bayer (1931) found that 8 out of 13 cases of cephalhaematoma had a low capillary resistance whereas in this investigation the months during which this lesion was found to be most common (May and June) are those in which the resistance is high.

AGE TRENDS

Bayer (1930) examined 52 babies, testing them all at a pressure of 220 mm.Hg. He found 52 to show petechiae at birth and none at the 10th day, concluding that a rise in capillary resistance

during the first few days of life is a normal feature in full-term babies. Lindquist (1937) on the other hand, using a smaller cup (1 cm.) testing up to 500 mm.Hg found no such trend over a 7-day period. Kugelmass (1940) stated that the resistance is high in infancy (550 mm.Hg) gradually falling to the adult level of 150 mm.Hg. Clement Smith (1951) quotes Bernfield (1931) as stating that the capillary resistance at "a few days" is high (600 mm.Hg) gradually falling to adult levels (250 mm.Hg to 400 mm.Hg) at the age of 2 years.

Little mention is made of tests performed within the first day or two of life, during which, according to Schwalm (1934), there is obvious histological development in the capillary bed. Abt *et al.* (1936), for example, state that the capillary resistance in the newborn is high, but did not test infants before the 3rd day of age. Munro *et al.* (1947) found no Rumple-Leede response below 3 months of age and state that there is a decline in capillary resistance "with age". They quote Ylppö (1924), Bayer (1930) and Maloney (1943) all as stating that the resistance rises in the first few days and gradually declines till the age of 2 years. The differing results in these reports could be caused by many factors, e.g. the inclusion of premature infants' results along with the mature, the use of negative or positive pressure methods, the size of the cup used, and the site chosen, and comparison of all these figures with the present series is not possible. Brock and Malcus (1934) found, for example, that in children capillary strength declined with age when the skin of the chest was tested, but it showed no such changes on the skin of the arm.

The age trends in capillary resistance under standard conditions seemed worthy of further investigation, and 622 test results obtained from newborn infants examined during their 8 to 10 days' stay in hospital were analyzed with this point in view. It soon became obvious that the pressure levels of tests done within the first 24 hours of life tended to be lower than those done after that time and that still higher pressures were required after the 5th day. The test results were, therefore, divided into three groups: (1) those tested under 24 hours of age; (2) those between 24 hours and 4 days, and (3) 5 or more days after birth. Table IV shows the numbers of cases positive at 100 mm.Hg or less and the numbers at 150 mm.Hg or more. The percentages are also tabulated. As no significant seasonal variation was detected, a composite figure was obtained in each group (Fig. 5).

TABLE IV

	Positive at 100 mm.Hg or less		Positive at 150 mm.Hg or more		
	No.	Per cent	No.	Per cent	Total
Below 24 hours ..	155	83	31	17	186
24 hours to 4 days ..	165	49	171	51	336
5 days and over ..	23	23	77	77	100
					622

It can be clearly seen that the younger the infant, the more fragile are the capillaries, at least within the age period covered. This correlation is statistically significant. One hundred and twenty-three test results were analyzed to elicit any change in resistance that might occur within the first 24 hours of life. It is known that the resistance can alter markedly within the time of a

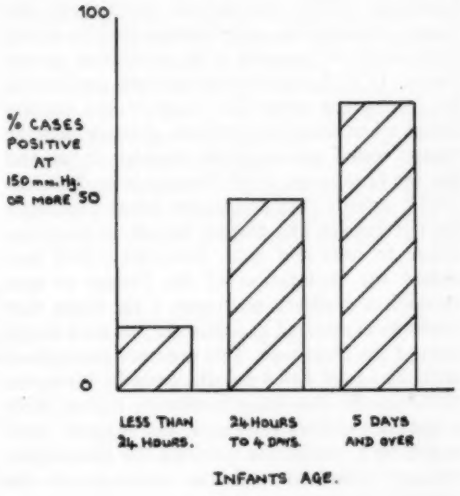

FIG. 5

surgical operation (Robson, 1949; Scarborough, 1944), and the question arose as to whether the infant capillaries respond to the factors initiating labour or to labour stress itself, and whether this response, if present, could be over within 24 hours of delivery. There appeared, however, to be a tendency for the capillary resistance to increase from birth onwards, though the results are in no way conclusive.

It is certain, however, that there is no initial high capillary resistance which could be missed if tests were not made within the first few hours of life. The infants had, as was suspected from previous findings, a low resistance at birth, which increased gradually during the neonatal period.

Prematurity

Although prematurity is best defined in terms of crown-rump length, there are as yet no universally accepted standards. The more convenient method of assessing the infant's maturity by weight was adopted.

Bayer (1930), Ylppö (1924), Lindquist (1937) and Minkowski and Venes (1948) are all agreed that there is a relationship between the birth weight and the capillary resistance, the lower the weight the lower the resistance. Bernfeld (1931) gives the results of 36 infants under 2·5 Kg. and concludes that there is no such relationship, but Lindquist (1937) re-examined the figures and found considerably more infants positive at the lower levels of pressure in the premature group. Sanna (1934) found that the nail bed capillary in the premature resembled that of the mature infant when tested by pressure changes, but the vessels tested were only the broader arches and not the finer loops which develop later. Eckstein (1933) reports that premature infant capillaries do not behave like mature vessels in their response to heat and cold. Schwalm (1934) described the maturation of the former as seen through a capillary microscope. He states that maturity is attained at about the 5th week in the skin of the chest wall. This does not correspond with the age of 2 to 3 months given by Lindquist (1937) as the date when premature infants show a mature capillary resistance, but suggests there might be a connection between the histological changes observed and the response of the capillary to suction.

The 34 premature infants examined during this investigation showed a marked increase in fragility as compared with the mature infants. As very few premature infants could be tested within the first 24 hours of life and as they were only tested weekly, the results were divided into those obtained under, and those over, one week and as before the percentage of cases positive at 100 mm.Hg or less compared with those positive at 150 mm.Hg or more. These results were tabulated against those obtained from mature infants between 24 hours and 4 days old in the case of the premature babies below 1 week, and mature infants of 5 days or more in the case of premature babies over 1 week (Table V).

Table V

	Positive at 100 mm.Hg or less		Positive at 150 mm.Hg or more	
Age	Less than 1 week	Over 1 week	Less than 1 week	Over 1 week
Premature	80%	57%	20%	43%
Age	1-4 days	5+ days	1-4 days	5+ days
Mature	49%	23%	51%	77%

Table V clearly shows that the premature infant, like the mature, has an increase in resistance with advancing age. Twenty per cent of premature infants of less than 1 week old had a positive result at 150 mm.Hg, whereas 43 per cent of infants over 1 week of age were positive.

This difference between mature and premature results in both age groups is statistically significant.

It may be concluded that the premature, though less resistant initially, showed the same increase in resistance with age as the mature infants. It was also noticed that the amount of bruising in premature infants was much greater and that it occurred without the appearance of petechiae on a number of occasions. This suggests that in these infants the suction was exerting its effect on a premature vascular bed in which the capillary, as seen in the older child, had not yet developed.

The exact nature of this discoloration is uncertain and no opportunity arose for examination of the skin lesion histologically. The absence of petechiae in some cases indicates that it is due to

a generalized dilatation of capillaries or, as suggested by Abt *et al.* (1936), to transudation of blood into the extravascular space from a deeper plexus and not to punctate capillary rupture. Whether this finding is an indication of undue capillary permeability rather than fragility is a point which must await further investigation. It can be concluded, however, that there is a definite relationship between bruising and the number of petechiae produced (i.e. the greater the number the more likely bruising is to occur).

The Effect of Birth-weight on Capillary Resistance in Mature Infants

Lindquist (1937) examined 106 mature infants and found that birth weight had no relation to capillary resistance. Two hundred and sixty-six mature infants in the present series were examined and the results tabulated (as shown in Table VI). This includes a few premature infants between 5 pounds and 5 pounds 8 ounces for completion of the 5 pounds to 5 pounds 15 ounces group. All the infants were tested between the age of 24 and 72 hours.

Examination of Table VI shows that in this series the direct relationship between resistance and birth weight is continued even within the mature group itself. Although the numbers of cases at the extremes of weight are small, there are sufficient to indicate a significant trend. The probability of these changes occurring by chance is about 1 in 20 (Fig. 6).

Re-examination of Lindquist's (1937) figures, however, shows a similar trend, the significance of which is lost owing to a single result. This result cannot be overlooked, but it is not unreasonable to suggest that its effect might have been offset had there been a larger number of cases in the series.

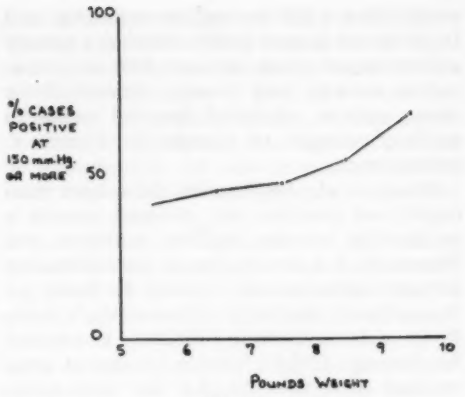

Fig. 6

Vitamin Deficiency and Capillary Resistance

Knowledge that the capillary resistance test was frequently positive in manifest and subclinical scurvy (György, 1927; Öhnell, 1928; Gothlin, 1931; Molitch, 1936) stimulated many later workers to investigate the effects of Vitamin C on capillary strength. Bell *et al.* (1940) found a significant rise in resistance after Vitamin C therapy when the initial resistance was low, but they could not correlate the petechial count of their positive pressure method with the plasma Vitamin C concentration. Abt *et al.* (1936), with a negative pressure method, came to the same conclusions, and Greene (1934) also doubts whether any resistance test is specific for clinical or sub-clinical scurvy. O'Hara and Hauck (1936) found no relationship between capillary resistance and the urinary excretion of Vitamin C. Gothlin (1937) nevertheless was able to determine that a blood concentration of Vitamin C of 1 mg. per litre or less

Table VI

	Pounds 5 to 5·15		Pounds 6 to 6·15		Pounds 7 to 7·15		Pounds 8 to 8·15		9 pounds+	
	No.	per cent	No.	per cent	No.	per cent	No.	per cent	No.	per cent
Positive at 100 mm.Hg or less ..	11	58	42	54	50	52	25	45	5	30
Positive at 150 mm.Hg or more ..	8	42	36	46	46	48	31	55	12	70
No. totals	19		78		96		56		17	

would effect a fall in capillary resistance, and Dalldorf and Russell (1935) observed a prompt and prolonged rise in resistance following intravenous ascorbic acid therapy. Several of the above authors attributed seasonal trends in capillary strength to changes in Vitamin C concentration.

Munro *et al.* (1947) review the subject thoroughly and conclude that, although there is a relationship between capillary resistance and Vitamin C, it is not as close as the relationship between resistance and Vitamin P. There are those who still dispute the existence of a Vitamin P or substances with Vitamin P activity. Scarborough (1939), however, produced good evidence to support the idea that some factor other than Vitamin C had an effect on capillary fragility. Ten years after his earlier work, Scarborough with Bacharach (1949) published a detailed account of the chemistry and pharmacology of Vitamin P and showed the relationship between it and Vitamin C with particular reference to capillary resistance.

Scarborough and Bacharach (1949) suggest that there are several distinct compounds containing the active group which is present in Vitamin P. These compounds are mostly flavones, the most well-known being Hesperidin (a flavonine glucoside), Rutin (a flavanol) and Citrin (a concentrated extract of citrous peel). These authors state that Citrin has the greatest Vitamin P activity, probably on account of its solubility. Johnson (1946) enumerated several conditions in which this vitamin had been tried in clinical practice and had 88 per cent (152 out of 173 cases) success in restoring the capillary resistance to normal. He insisted that the Vitamin C intake must be adequate, as this vitamin was apparently required to "activate" Vitamin P. Cotereau *et al.* (1948) discuss the relationship between Vitamins C and P and suggest that Vitamin P is a Vitamin C-sparing factor and that the latter cannot control capillary resistance in the absence of this factor (Vitamin P) in the guinea-pig. Vitamin P alone had no marked effect on the resistance, but the administration of it reduced the body requirements of Vitamin C. Analysis of animal tissue showed that no storage of Vitamin C occurred in the absence of this sparing factor.

Ambrose and De Eds (1947) support the view that Vitamin P on its own has no effect on capillary function. They found Rutin had no effect on the high capillary permeability in scorbutic guinea-pigs, but that it did decrease permeability in rabbits.

Munro *et al.* (1947) were not convinced that Vitamin P reduced the body's need of Vitamin C, but found that Vitamin P, though not apparently essential to life, improved the capillary strength even when the diet was normal. They found that scorbutic guinea-pigs, which did not respond to Vitamin C alone, did so when Vitamin P was added to the diet. Finally, they suggest that the mechanism by which these vitamins act is to prevent the oxidation of adrenaline. In scurvy, there is a lack of collagen supporting tissue and vascular atonia. The vitamins delay the destruction of adrenaline, which in turn increases capillary tone and diminishes the tendency to rupture.

Kugelmass (1940) found that Vitamin P had definite effects on purpura of nutritional, allergic or infective origin in children. No effect was observed in purpura of mechanical origin. Only one other work could be found in which children had been examined. Minkowski and Venes (1948) gave Esculoside (a substance with Vitamin P activity) to 2 mothers at term. The newborn infants showed a low capillary resistance which was unexplained. Seven premature infants given the vitamin showed a significant increase in capillary resistance.

It is unlikely that the newborn baby lacks an adequate supply of Vitamin C. Lund and Kimble (1943), whose work has been confirmed by Slobody, Benson and Mestern (1947), investigated 94 babies and found that 21 per cent had plasma Vitamin C levels below 1·0 mg. per cent and that 7 per cent had levels below 0·6 mg. per cent. As 50 per cent of the mothers had levels below 0·6 mg. per cent, they suggest that the placenta exerts a selective retention of Vitamin C easily available to the foetus. Abt *et al.* (1936) found mother and infant to have similar blood concentrations.

Investigations of Antenatal Vitamin P Prophylaxis

As the mothers in the following investigation were all on approximately standard diets con-

taining Vitamin C supplements and as it appears from the above that the foetus is assured of an adequate Vitamin C supply, it was decided to investigate the effects of Vitamin P alone on the capillary resistance of newborn infants.

Thirty women were given 60 mg. Vitamin P 3 times daily for at least the last 4 weeks of pregnancy. Twenty-seven others were taken as controls and were a strictly comparable group, apart from the vitamin therapy. All the women were primiparous. At the onset of therapy, they were entirely free from any complication of pregnancy, and both groups were given the same dietary regime. Capillary studies were made on the mothers before, during, and after labour, the results of which are reported elsewhere (Walker and Balf,1952). The vitamin was discontinued at term. The concentration built up in the maternal circulation would be maintained for about 3 days (Scarborough, 1945). After this time, any fall in resistance could be due to withdrawal of the vitamin. No evidence is available to indicate the amount of Vitamin P in breast milk nor is it certain that this dosage increases the maternal blood level of Vitamin P or the total tissue storage.

During the investigation, one mother in the Vitamin P group developed mild hypertension shortly before term; one had a discharging dental sinus, and one a septic polyp in the right ear. In the control group, one developed mild pre-eclamptic toxaemia, and one mild hypertension. The infants born of these mothers were, however, included in the calculations as the infants were clinically normal at birth, and it was considered that the effects, if any, of these conditions on the infants (and their capillaries) would be approximately the same in each group. One infant was stillborn in each group, leaving a total of 55 live babies.

Table VII shows the results of 182 tests on these 55 babies. The results are tabulated according to the pressure at which the test was positive and the age (in days) of the infant when tested. The results of those given Vitamin P are tabulated alongside the controls for the purposes of comparison. No statistical difference can be shown between the two groups. On the first day 84 per cent of the Vitamin P group were positive at 100 mm.Hg or less, compared with 73 per cent in the control group. On the fourth day 57 per cent of the Vitamin P group were positive at 150 mm.Hg or less, compared with 55 per cent in the control group.

Vitamin K. Vitamin K prophylaxis and its relation to hypoprothrombinaemic haemorrhage in the newborn has been adequately reviewed by Potter (1945). That haemorrhagic disease at this age is sometimes due to a factor or factors other than, or in addition to, Vitamin K has become widely recognized.

TABLE VII

Number of Tests Positive at Various Pressures

Age (days)	Total Numbers		50 mm.Hg.				100 mm.Hg				150 mm.Hg				200+ mm.Hg			
	P	C	P		C		P		C		P		C		P		C	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1	25	22	7	28	9	41	14	56	7	32	3	12	3	14	1	4	3	14
2	7	10					3	43	5	50	2	28	3	30	2	28	2	20
3	7	14	1	14			1	14	6	43	5	72	7	50			1	7
4	14	9					3	21	3	33	5	36	2	22	6	43	4	45
5	9	6					3	33	1	17	4	45	4	66	2	22	1	17
6	3	12			1	8			6	50	1	33	2	17	2	66	3	25
7	11	8					1	9	2	25	5	45	3	37	5	45	3	37
8	6	9					1	17	2	22	4	66	5	56	1	17	2	22
9	1	1					1										1	
10	7	1					2	29			3	42	1		2	29		

P=cases given Vitamin P
C=controls.

Some of the literature concerning the effects of Vitamin K on intracranial haemorrhage has been quoted above. Very little, however, has been published concerning the effects of this vitamin on capillary resistance. In 252 cases it was noted, therefore, whether the infant received the vitamin. It should be mentioned that the vitamin was given only when the infant was delivered instrumentally or showed signs of shock or cerebral irritation at birth.

It is clearly seen from Table VIII that there is

TABLE VIII

	Vitamin K (5 mg.)		Controls	
	No.	per cent	No.	per cent
Positive at:				
50 mm. Hg	7	19	33	15
100 ,, ,,	12	33	75	35
150 ,, ,,	12	33	71	33
200+ ,, ,,	5	16	37	17
	36		216	

no demonstrable change in capillary resistance. It is possible that these cases might have shown capillary resistance changes had the vitamin not been given. It is more likely, however, that neither the mode of delivery nor the vitamin had any influence on the capillary fragility.

It does not appear that any great difference in capillary resistance during the first week of life can be correlated with the administration of Vitamin K under the conditions of this experiment.

Relationship of Capillary Resistance to Peripheral Circulation

Close observation of an infant during the first few days of life reveals that considerable change in colour and temperature of the extremities can occur. Lindquist (1937) studied "neonatal erythema" which he states as being maximal at 24 to 48 hours after birth. He considers this colour change to be a response to the cold extrauterine environment, but observed it in only 43 out of the 108 cases examined. He compared the capillary resistance by observing the percentage of cases positive up to 500 mm.Hg in the erythema cases and a control group of different ages and found no appreciable difference.

Peripheral cyanosis is indicative of local anoxia. Henry, Goodman and Meechan (1947) found oxygen saturations below 15 per cent and possibly even 25 per cent increase capillary permeability. That capillary permeability and fragility are separate entities is stressed by Ambrose and De Eds (1947), but they also state that an increase or decrease in the one is roughly proportional to similar changes in the other. It is of importance to note also that Clement Smith (1951) on examining 31 newborn infants found oxygen saturations below the 15 to 25 per cent level in 20 out of 121 (16·5 per cent) occasions. On the other hand, Hopps and Lewis (1947) found that anoxic anoxia in guinea-pigs did not influence capillary permeability to globulin, and suggest that positive results obtained when stagnant anoxia is present are due to carbon dioxide excess damaging the capillary and not to oxygen deficiency. Ninety-seven cases were, therefore, analyzed to see if there was any relationship between capillary resistance and peripheral cyanosis (Table IX).

TABLE IX

Relation of Capillary Resistance to Peripheral Cyanosis

Pressure mm.Hg	Cyanotic (26)		Acyanotic (71)	
	100 or less	150 or more	100 or less	150 or more
No.	16	10	49	22
Per cent	62	38	69	31

As the peripheral cyanosis in these normal infants is almost certainly due to stagnant anoxia, it can be concluded that the capillary resistance in the skin is not influenced by anoxia of this severity and duration. This conclusion cannot be extended to the effects of visceral venous stagnation since the skin is cool and metabolism accordingly must be very low.

Miscellaneous Results

In addition to the above analyses, 258 results (137 males and 121 females) were examined and no difference in the capillary resistance between the sexes was observed. Of 254 cases in which the mode of delivery was noted, only 23 were

delivered instrumentally. They showed similar resistance results to those obtained from the spontaneously delivered infants. Jaundice, observed in 79 cases, did not appear to alter the resistance. It is, therefore, concluded that sex, jaundice, and mode of delivery have no influence on the resistance under the conditions of this experiment.

Conclusions

The lack of uniformity in published accounts of capillary studies in the newborn makes detailed comparison with previous work impossible. Since minor differences in technique appear so important, it could be argued that quite distinct physiological functions were being measured. Nevertheless, we believe that comparison of the trends reported by various authors is justifiable.

The absence of any marked seasonal trend in capillary resistance in the newborn contrasts with adult experience. Standard vitamin supplements are issued to all expectant mothers in this country and this may well overcome seasonal shortages in the diet. There is, in addition, evidence that the foetus stores Vitamin C effectively even though the maternal intake is low. Moreover, climatic and other environmental factors, which may influence capillary function in the adult through adrenal responses, cannot affect the foetus except through the maternal circulation. The isolation of the foetus *in utero* from external factors is such that the results of physiological tests at birth will depend chiefly on the maturity of the infant and on the presence of circulating agents released through the placenta during the process of birth itself.

There is no evidence that fatal intracranial bleeding shows a seasonal trend in this city, apart from the small group of stillbirths with subarachnoid and intraventricular bleeding. The trend here, however, is so well-marked that it almost endows significance to the seasonal figures for all haemorrhages other than subdural. Kerpel-Fronius *et al.* (1948) have not analyzed their figures in detail and quote merely a total for all clinical and post-mortem cases of cerebral haemorrhage. Moreover, climatic and social differences make a direct comparison between Edinburgh and Pécs unsatisfactory. Dam *et al.* (1952) found a definite seasonal trend in intracranial haemorrhage in premature infants in Holland and their figures are compared with the seasonal incidence of subarachnoid and intraventricular haemorrhage in the present series below (Table X).

Table X

	Jan. to Mar.	April to June	July to Sept.	Oct. to Dec.	
Dam *et al.*	78	88	57	27	All premature
Present series	81	121	92	85	Subarachnoid and intraventricular haemorrhage only

The demonstration that in the present series this trend occurs only in the stillbirths is of interest in relation to the contention by Dam *et al.* (1952) that certain degrees of intra-uterine asphyxia are associated with extreme prolongation of the prothrombin time. They suggest on this evidence that Vitamin K prophylaxis may prevent some forms of intracranial haemorrhage. No evidence is yet available to indicate that such treatment reduces foetal mortality. It may be that asphyxial deaths are accompanied by less haemorrhage when Vitamin K is given.

It should be noted that the capillary studies here reported lend no support to the view that Vitamin K might influence capillary function nor could any relationship be established between capillary function and prolonged labour or intrauterine anoxia. Direct evidence is lacking to show that primary coagulation defects imply an increasing risk of spontaneous haemorrhage after birth, but it is apparent that any defect in haemostasis must increase the severity of traumatic or asphyxial bleeding.

Capillary Resistance in Relation to Maturity

Capillary resistance both at birth and during the neonatal period is closely related to birth weight. The higher mortality of premature babies and the frequent occurrence of fatal haemorrhage lesions in this group still, therefore, merits further comment. There is little doubt that skin capillaries in such infants are morphologically (Sanna, 1934) and functionally

(Eckstein, 1933) different from those in mature infants and it must be accepted that the trend in resistance parallels increasing development of the capillary bed and that within certain limits the risk of capillary haemorrhage is strictly defined by the period of gestation.

Since it appears that Rutin (Vitamin P) and Vitamin K do not influence capillary resistance under the conditions of our investigations there seems no case for the routine administration of these substances to control post-natal bleeding. Proof of the efficient control of asphyxial coagulation defects by ante-natal Vitamin K would provide a certain indication for routine administration. Minkowski (1951) suggests that Vitamin E in high dosage increases the capillary resistance when given to premature babies. Since this substance passes the placenta freely it has also been given during labour and evidence has been published indicating that this has a definite effect on the capillary resistance of premature babies and reduces the incidence of foetal haemorrhage. No confirmation of this work is yet available. It should be noted that the dosage used suggests this is a pharmacological effect rather than the correction of some dietary deficit.

Since the capillary resistance in both mature and premature babies increases with age and since this change is more rapid in the early days it is possible that normal labour exerts an influence on the vascular bed by some agent crossing the placenta or formed within the foetus. The post-natal rise in capillary resistance is probably too rapid to be explained by known degrees of histological maturation of the capillary bed.

Post-natal changes in serum concentrations of oestrogens are held to account for delayed vaginal bleeding in the newborn and breast hypertrophy. Rapid reduction of blood oestrogen levels during labour and the early puerperium is accompanied by a marked rise in the capillary resistance in the mothers. Evidence that oestrogens directly affect capillary resistance, however, is conflicting. In dogs, high dosage of oestrogen reduces capillary resistance (Skelton *et al.*, 1946) and rarely clinical reports of oestrogenic bleeding controlled by progesterone have appeared (Minkowski and Venes, 1948). Further clinical investigation of the relation between blood or urine oestrogen levels and capillary resistance should probably await the final determination of reliable methods of hormone assay. It would seem strange that an obligatory accompaniment of normal labour should incapacitate the foetus during its hazardous passage by ensuring a dangerous weakness of the capillary bed.

The participation of other steroid hormones cannot be excluded. In the limited analysis of such cases in the present series no relationship could be established between abnormal labour and capillary resistance at birth. It is not possible to exclude the participation of foetal adrenal response to injury by this means since there is at present no accurate means of assessing foetal risk *in utero*. Neither forceps delivery itself nor simple prolongation of the second stage are adequate measures in a short series, but it seems reasonable to suppose that only exceptional disturbances *in utero* would alter the capillary resistance by such means. Despite morphological evidence of adrenal atrophy after birth it seems that steroid excretion increases (Klein, 1951) and that eosinopenia is more reliably produced by adrenaline after the first week of life. Uncertainty of the relationship of these changes to the rôle of steroid hormones in controlling capillary resistance restricts further discussion. Although capillary resistance in the adult can be raised by Cortisone or ACTH there is as yet insufficient evidence to suggest that variations in adrenal activity alone control the post-natal changes in capillary resistance in newborn babies.

Marked fragility of peripheral capillaries in premature babies exists independently of such physiological considerations. We feel that structural weakness here is of such importance that transient humoral effects can have little influence on the clinical outcome. Asphyxia, however, may favour fatal haemorrhage either visceral or intracranial, but trauma, as such, plays little part except in massive subdural bleeding. Venous congestion adds stagnation of metabolic products to simple anoxia. The distribution of visceral venous congestion in asphyxia suggests active vasomotor adjustments akin to shock (Gruenwald, 1950) so that local haemorrhage may depend on local vascular disturbances

of such severity that they outweigh even the demonstrated variability in capillary resistance. Nevertheless, additional chemical agents favouring capillary rupture must add to the gravity of any degree of anoxia or local stagnation. Capillary resistance is known to be lowered by the intravenous injection of histamine (Robson and Duthie, 1950) and during anoxia blood histamine levels are raised. Cord blood contains more histamine than adult blood, possibly because histaminase activity is low (Kapellar-Adler, 1953). If foetal anoxia increases the blood histamine level to effective concentrations then it seems possible that a transient reduction in capillary resistance will occur and this will return to normal as the histamine is destroyed. Further studies are necessary to elucidate this relationship. Since anti-histaminics are known to raise capillary resistance (Parrot, Galmiche and Richet, 1945) it seems possible that treatment of the mother with a preparation capable of crossing the placenta may prevent any haemorrhages caused by local excess of histamine.

Summary

(1) Capillary resistance tests in infants and adults are reviewed and the importance of minor differences in apparatus and procedure are demonstrated.

(2) In the newborn the critical pressure for petechiae decreases with increase in size of the cup used.

(3) A direct relationship was observed in infants between bruising and oedema and the number of petechiae produced.

(4) No definite seasonal trend exists in the newborn.

(5) Only 9 per cent of cases of intracranial haemorrhage show a definite seasonal variation. These were all stillborn infants who had subarachnoid or intraventricular haemorrhage. The incidence was highest in the second quarter of the year coinciding with the time at which infants aged 1 to 4 days appear to have a lower capillary resistance, but not with the trend in infants up to 24 hours of age.

(6) There is a significant increase of resistance from birth, when it is at its lowest, till the end of the first week of life—the end of the period of observation.

(7) Premature infants have a lower initial resistance, but show a similar increase with advancing age.

(8) The resistance increases with increasing birth weight even in mature babies.

(9) There is no difference in capillary resistance between the male and the female infant.

(10) Ante-natal Vitamin P has no significant effect on the capillary resistance of newborn infants.

(11) The mode of delivery, the giving of Vitamin K, and the presence, or absence, of jaundice did not appear to influence the resistance.

(12) Peripheral cyanosis does not affect capillary resistance.

(13) It is concluded that the maturity of the capillary bed at birth is of primary importance in determining the capillary resistance and that the physiological effects of oestrogens, steroids and possibly histamine may influence early postnatal changes.

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CAPILLARY RESISTANCE STUDIES

Part II: Late Pregnancy, Labour and Early Puerperium

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INTRODUCTION

DURING the course of a large-scale investigation of the capillary resistance in infants (Walker and Balf, 1954) the opportunity presented itself of testing a number of mothers antenatally, during labour and the early puerperium. In addition, permission was obtained to test a number of the nursing staff who acted as non-pregnant controls. It is the purpose of this paper to report on the investigations of the mothers and nursing staff.

METHOD

The details of technique and the reasons for adopting the particular method used during these investigations have been discussed in detail (Walker and Balf, 1954). One or two points of difference between the infant and adult tests and between the method chosen for these experiments and some used by other authors are worthy of reiteration.

The principal difference between the infant and adult tests was the site chosen. In the adult, the volar aspect of the forearm was used and the medial aspect just distal to the elbow crease was first tested (Area "A"). In the early stages the lateral aspect (Area "B"), and the area just proximal to the wrist joint (Area "C") were tested but later (particularly during labour) only Area "A" was used so that the patient was as little disturbed as possible. The time of each exposure was 1 minute and not 30 seconds as described by Brewer (1938), Scarborough (1941), and Robson and Duthie (1950). The critical pressure was as described by Robson and Duthie (1950), i.e. the pressure at which 1 to 10 petechiae were produced. These authors examined their cases at the same time of day in order to offset any diurnal variations. Munro, Lazarus and Bell (1947) also state the necessity of doing serial resistance tests at a fixed time of day owing to an apparent decrease in strength as the day advances. This was not possible in the present series on account of the varying time of birth of the infant. The initial post-partum reading was taken, therefore, at any time of the day or night, but tests thereafter were usually performed between 10 a.m. and 12 noon. In addition to the antenatal tests (all performed between 2 and 4 p.m.) and the intra-partum tests (done at any time of day or night) most mothers had a test performed as soon after labour as was possible and thereafter 2 or more further tests were done at 2-day intervals according to the duration of stay in hospital.

The normal adult variations relative to age (Walker and Balf, 1954; Cutter and Marquardt, 1930; Dalldorf, 1933; Tey, 1940; Brown, 1947; Munro *et al.*, 1947), season (Walker and Balf, 1954), time of day (Walker and Balf, 1954; Robson and Duthie, 1950) and menstruation (Stephan, 1921; O'Hara and Hauck, 1936; Brewer, 1938; Bell, Lazarus and Munro, 1940) have been adequately studied. The mothers tested were, therefore, all between 20 and 30 years of age only, as it was considered that the change within a 10-year period would be too small to affect the results. The tests were, except

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for a few non-pregnant controls, done within a period of 4 months. It was considered unnecessary to obtain details of the menstrual state of the non-pregnant controls as there was a sufficiently large number to obtain a fair average.

The Effects of Normal Pregnancy, Labour and Puerperium on Capillary Resistance

McLennan (1946) and Browne (1944) have noted an increase in capillary permeability in later pregnancy.

Minkowski and Venes (1948) found the resistance lowest at full dilation of the cervix during labour, and also found, on examination of 37 women, that there was a slow post-partum rise in resistance reaching normal within a few weeks. Gianaroli (1945) also found the resistance to be lowered during pregnancy, especially towards term, and returning to normal within 3 months.

Dieckmann, Akbasli and Aragon (1949) state the normal capillary resistance to be 200 to 250 mm.Hg and examined 164 cases showing pregnancy hypertension or toxaemia by both negative and positive pressure tests. The results are mentioned below. Robson and Duthie (1950) give 250 to 350 mm.Hg as the average range for their method which is similar to the one used in this experiment except for the method of lighting, magnification, and the time of exposure.

Roberts, Griffith and Kimbrough (1944) testing women during pregnancy found an abnormal increase in capillary pressure after histamine injection and increased cutaneous lymphatic flow, and found the actual capillary count to be normal in most cases. Browne (1944) found an increase in capillary pressure in later pregnancy in the lower limbs. Bean *et al.* (1947, 1949) report the observation of vascular spiders and palmar erythema from the second month of pregnancy, the spiders increasing in number till term. These were present in 65 per cent of white women with uncomplicated pregnancies and disappeared mostly within the first week of the puerperium. Some spiders, however, were observed till about the 7th week after delivery.

It was decided, in view of these interesting observations, to analyze the maternal results and see if an ante-partum fall and post-partum rise in capillary resistance could be demonstrated. As Vitamin P has been shown to have no significant effect on maternal capillary resistance (see below), the Vitamin P treated and the untreated cases were taken as one group to be compared with the non-pregnant controls.

Seventy-four non-pregnant controls were each tested on one occasion and the results divided into (1) those positive at 150 mm.Hg or less; (2) those positive at 200 mm.Hg and (3) those at 250 mm.Hg or more. Table I shows the detailed analysis of these results.

Table I

	Critical Pressure (mm.Hg)				
	100−	150	200	250	300+
Nos. ..	3	13	45	7	6
Nos. ..	16		45	13	
Per cent	21·6		61·4	17	

These controls might be expected, when tested for 60 seconds, to have a lower average pressure reading than those tested for 30 seconds by other workers and this is indeed the case.

These results were compared with 174 Area "A" test results performed on 57 mothers during their last 6 weeks of pregnancy. Their results were analyzed in the same way as the non-pregnant control findings (Table II) and the composite Table III shows the comparison.

Table II

Time before term	Critical Pressure (mm.Hg)					Totals
	100	150	200	250	300+	
6 weeks ..	—	5	9	2	—	16
5 weeks ..	1	9	8	2	—	20
4 weeks ..	1	11	11	8	1	32
3 weeks ..	4	6	14	2	2	28
2 weeks ..	3	10	9	10	2	34
1 week ..	3	12	19	9	1	44
Nos. ..	65		70	39		174
Per cent ..	37·4		40·2	22·4		

During the week immediately before term, when the resistance is reputed to be at its lowest, 44 tests were made. The analysis of these 44 tests is shown in the composite Table III in addition to the percentage positive tests in the

3 stated groups in 1-week periods. The numbers in the 5th and 6th immediate antenatal weeks were too small to be of value.

From the foregoing Tables it can be seen that there is a definite difference in the percentage distribution of tests when the expectant mothers' results are compared with those of the non-pregnant controls.

In Area "A" there is a very definite spreading of the distribution, cases "leaving" the 200 mm. Hg group and going to both the lower and higher pressure groups. The percentage incidence in the 200 mm.Hg group being 61·4 per cent in the case of the controls and only 40·2 per cent when the findings for the last 6 weeks of pregnancy are taken as one group in the case of the pregnant women.

The individual results for the 4 weeks just prior to term show a similar trend. They, in fact, indicate a significant fall in capillary resistance as term is reached. The percentage incidence in the 150 mm.Hg group is approximately the same in all 4 antenatal weeks which suggests that the changes take place before this period of gestation. The spread into the 250 mm.Hg group is not significant. Analysis of Area "B" results support these findings.

The effects of labour and the changes (if any) in capillary resistance during the puerperium of the 57 women were assessed in a similar manner. In Area "A" a further 267 natal and postnatal test results were added to the 174 antenatal readings and these 441 results divided into the same 3 pressure groups as shown above. A composite Table showing the incidence antenatally (during the last 6 weeks of pregnancy), during labour, and postnatally (during the 8 to 10 days' stay in hospital) was constructed. In Area "B" a further 238 test results were added and the total 365 results analyzed and tabulated similarly (Table IV).

It can be clearly seen from Table IV and Fig. 1 that both Areas "A" and "B" show a definite natal and postnatal shift towards the higher pressure groups, and that in the puerperal phase there are a great many more tests positive in the

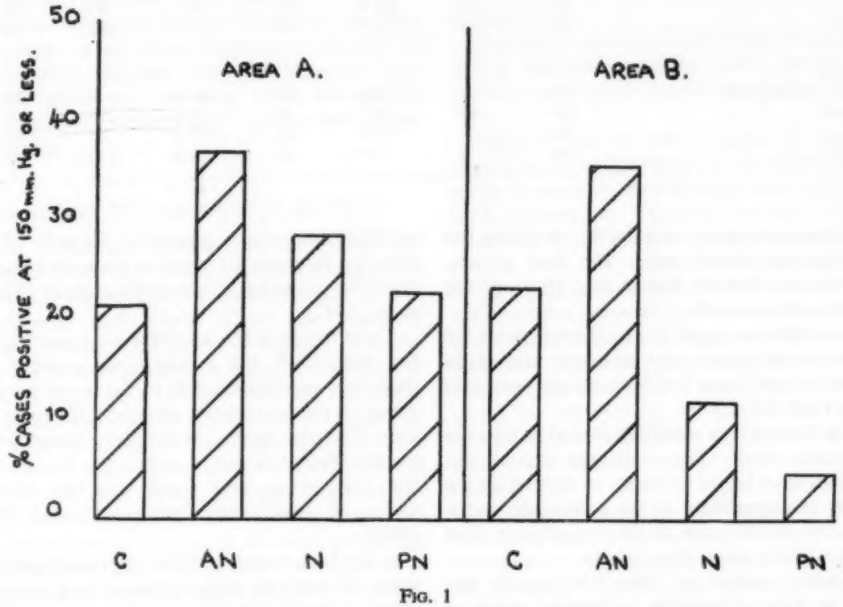

FIG. 1

C = Control. AN = Antenatal. N = Natal. PN = Postnatal.

TABLE III

	No.	Critical Pressures (mm.Hg) 150 mm. or less	200 mm.	250 mm. or more
AREA "A"		per cent	per cent	per cent
Non-pregnant controls	74	21·6	61·4	17
Minus complications per cent	157	35·6	42·0	22·3
Total 6 weeks before term	174	37·4	40·2	22·4
1st week before term	44	34·0	43·2	22·8
2nd week before term	34	38·2	26·5	35·3
3rd week before term	28	35·7	50·0	14·3
4th week before term	32	37·5	34·4	28·1

TABLE IV

	Total Nos.	Critical Pressures 150 mm.Hg or less		200 mm.Hg		250 mm.Hg or more	
		No.	Per cent	No.	Per cent	No.	Per cent
AREA "A"							
Control: non-pregnant	74	16	21·6	45	61·4	13	17
Antenatal	174	65	37·4	70	40·2	39	22·4
Natal	83	24	28·9	29	35	30	36·1
Postnatal	184	42	22·9	40	21·7	102	55·4
AREA "B"							
Control: non-pregnant	30	7	23·3	14	46·6	9	30
Antenatal	127	42	33	30	23·6	55	43·3
Natal	68	8	11·8	18	26·5	42	61·7
Postnatal	170	8	4·7	32	18·8	130	76·5

highest pressure group than are found among the non-pregnant control cases. The final percentages are significantly higher than those of the non-pregnant controls.

An attempt was made to see at what point the maximum resistance was reached and daily analysis of the Area "A" puerperal tests was made (Table V).

Table V shows no significant trend within the puerperium itself. The resistance would not appear to have begun to return to normal by the 8th day of puerperium as the percentage distribution up to this age is very similar to that obtained a few hours after labour.

A similar analysis of Area "B" results was made to find, if possible, a turning point at which the capillary resistance begins to fall. This analysis was again necessary because of the differing response to negative pressure obtained on different areas of the body surface (Munro *et al.*, 1947).

Unfortunately, the numbers were smaller than for Area "A", but it was again obvious that there was no definite shift to the lower pressure group as the puerperium advances. It can be said then that the return of capillary resistance to normal does not occur within the 1st week of the puerperium, thus supporting the views of Gianaroli (1945) and Minkowski and Venes (1948).

It has been mentioned that the results obtained from 12 mothers with antenatal and postnatal minor complications were included in the above analysis. Inspection of the individual result

TABLE V

Time	Total Nos.	Critical Pressures					
		150 mm.Hg—		200 mm.Hg		250 mm.Hg+	
		No.	Per cent	No.	Per cent	No.	Per cent
AREA "A"							
Few hours	17	5	29·5	4	23·5	8	47·0
1+ day	33	8	24·2	8	24·2	17	51·5
2 days	18	2	11·1	5	27·8	11	61·1
3 days	22	7	31·8	3	13·6	12	54·5
4 days	24	4	16·6	6	25·0	14	58·4
5 days	11	2	18·2	3	27·3	6	54·5
6 days	23	9	39·1	3	13·1	11	47·8
7 days	17	1	5·9	1	5·9	15	88·2
8 days	13	4	30·8	4	30·8	5	38·4

revealed no difference between the "complicated" and normal women and further analyses similar to Tables III, V and VI showed no difference when the "complicated" cases were excluded. This finding is in the main in agreement with Dieckmann *et al.* (1949) who found that only 5 per cent of 63 patients with pre-eclamptic toxaemia had an abnormal capillary resistance. They also found that of the 75 hypertensive patients only 14 per cent had frankly abnormal resistance while another 22 per cent had results which were considered as borderline.

Vitamin P and Maternal Capillary Resistance

The literature concerning the effects of Vitamin P therapy on capillary resistance has been fully discussed by Walker and Balf (1954). Minkowski and Venes (1948) are the only workers found who gave a Vitamin P preparation to women during an uncomplicated pregnancy. They gave 40-100 mg. of Esculoside during the early stages of labour and found that in "5 out of 10 cases the capillary resistance rose 100 points". Dieckmann *et al.* (1949), on the other hand, gave 20 mg. of Rutin 3 times a day to 13 patients with so-called "abnormal capillary fragility" during the course of some pregnancy complication. They found that the resistance in 12 cases increased and in the 13th it diminished. In this investigation 30 pregnant women were given 60 mg. 3 times daily of this vitamin during the last 4 to 6 weeks of pregnancy and their capillary tests were compared with those of 27 controls of the same age and parity but not having the vitamin. Three patients in the Vitamin P group could not be tested at all and, therefore, there remain 27 patients in each group. A total of 414 Area "A" and 365 Area "B" tests were performed.

The results are tabulated (Table VI) as before, and a comparison thus made between the vitamin and control groups for Area "A" and "B".

Table VI shows that Vitamin P does not appear to have any effect on the capillary resistance at any time during pregnancy, labour and early puerperium. There is, in fact, a striking similarity between the two sets of results, the rise in both the vitamin and control groups being significant. It was for this reason that in the preceding sections the Vitamin P and control cases were considered as one group. It is possible that the obvious increase in capillary resistance obtained by Minkowski and Venes (1948) on giving the vitamin was, in fact, the rise obtained during the normal labour and puerperium (see above) and that it was not due to the vitamin therapy.

Another method of assessing the effect of Vitamin P on the capillary resistance is to divide the cases into 3 groups; the 1st group consisting of all cases showing an appreciable rise in capillary resistance during the period of examination (i.e. 100 mm.Hg or more); the 2nd group

TABLE VI

	Total Nos.	Critical Pressure					
		150 mm.Hg—		200 mm.Hg		250 mm.Hg+	
		No.	Per cent	No.	Per cent	No.	Per cent
AREA "A"							
Non-Pregnant controls	74	16	21·6	45	61·4	13	17·0
Antenatal: Vitamin P	58	21	36·2	31	53·4	6	10·3
Controls	89	35	39·3	31	34·8	23	25·8
Natal: Vitamin P	40	9	22·5	19	47·5	12	30·0
Controls	43	15	34·8	10	23·3	18	41·9
Postnatal: Vitamin P	89	22	24·7	14	15·7	53	59·5
Controls	95	20	21·0	26	27·4	49	51·6
AREA "B"							
Non-pregnant controls	30	7	23·3	14	46·6	9	30·0
Antenatal: Vitamin P	50	19	38·0	13	26·0	18	36·0
Controls	77	23	30·0	17	22·7	37	48·0
Natal: Vitamin P	31	6	19·4	7	22·6	18	58·0
Controls	37	2	5·4	11	24·0	24	64·9
Postnatal: Vitamin P	73	7	9·6	15	20·5	51	69·9
Controls	97	1	1·0	17	17·6	79	81·4

consisting of all cases showing a fall of similar dimensions; and the 3rd consisting of the cases showing no change at all or a rise or fall of only 50 mm.Hg. In each group, the Vitamin P and control cases were tabulated separately (Table VII).

There appears to be a difference between the Vitamin P and control group which is, however, not significant. At least it can be said that the Vitamin did not increase the resistance in the pregnant women in this series.

The mean initial resistance in the two groups is approximately the same so the apparent failure to rise of the cases in the Vitamin P group is not due to a higher initial resistance. It was considered justified in the light of these results to combine the groups for certain other analytical examinations.

Clinical Course in Relation to Maternal Capillary Resistance and Vitamin P Therapy

It is not unreasonable to suggest in the light of previous discussion that Vitamin P may be related to haemorrhagic conditions, the type of "haemorrhage" in question at the moment being blood loss during labour and the duration of red lochia during the puerperium. The cases were, therefore, divided as in the previous section and only changes of 100 mm.Hg or more were considered as important, thus increasing the accuracy of the observations. The 27 vitamin and 27 control cases were divided into the three groups and further sub-divided into those showing normal, moderate or excessive blood loss at labour. They were also divided into those with red lochia of 3 plus days or less than 3 days' duration.

TABLE VII

	Rising		Falling		No change		Total
	No.	Per cent	No.	Per cent	No.	Per cent	
Vitamin P cases	10	37·1	1	3·7	16	59·2	27
Control cases	16	59·2	3	11·1	8	29·7	27

Irrespective of the trend in the maternal resistance it was seen that approximately the same number of Vitamin P cases (18) had a normal blood loss as did controls (21). The same relationship is maintained among the cases with moderate loss.

Thirty-three cases had red lochia of more than 3 days' duration, 17 controls and 16 vitamin cases. This again shows no over-all difference and it is noticed that only 7 out of 17 cases in the group showing a rise were Vitamin P cases. The same proportions exist, however, among the cases with red lochia for less than 3 days.

The analysis, therefore, suggests that there is no relationship between a rise in resistance and the duration of red lochia. It also shows that there is no relation between the capillary state and the amount of blood lost during labour. It suggests that the Vitamin P cases may have a tendency to greater loss than the controls. These findings, however, are not statistically significant and may well be due to chance variation.

Capillary Resistance and Type, Duration and Period of Gestation of Labour

It has been clearly shown by Robson (1949) and Scarborough (1944) that there is a definite capillary response to operation, the post-operative resistance being measurably greater than the pre-operative. Labour itself might be considered as a "physiological operation" involving tissue damage and blood loss and it has definitely been shown above that a rise in resistance occurs during, and after, labour. Two further points require clarification. Does obstetrical operative interference still further increase the capillary resistance? And if it does, is this factor influencing the results of the group of tests as a whole?

Table VIII gives the comparison of cases entirely normal obstetrically with cases in which operative measures, including episiotomy, were required.

It can be concluded from this analysis that the effects of added obstetrical interference (if present) are not sufficient to enhance to any great extent the normal upward trend of resistance found in the patient delivering herself spontaneously. It seems unlikely, therefore, that the inclusion of these abnormal deliveries will invalidate the results. It is interesting to note that the only Caesarean section delivery in the series showed literally no increase in resistance throughout the test period; a case in which it would be reasonable to expect the resistance to rise.

Other factors than mode of delivery of the foetus and placenta must be concerned in the normal rise which occurs during parturition.

A similar analysis was performed dividing the cases into those with a labour of 15 or more, 10 or more, and less than 10 hours duration. Again, no relationship between duration of labour and resistance could be demonstrated.

Finally the cases were divided into groups according to the period of gestation at which labour took place. It was realized that estimation of gestational stage is often inaccurate but as far as could be assessed by current methods there was no difference in capillary resistance between those mothers going into labour before, at or after 40 weeks gestation.

TABLE VIII

	Critical pressure trend						Totals
	Rise		Fall		No change		
Delivery	P	C	P	C	P	C	
Spontaneous	5	11	—	2	8	6	32
Operative	5	5	1	1	8	2	22
Total	10	16	1	3	16	8	54

Key: P=vitamin P cases; C=controls.

TABLE IX

Infant critical pressure	Maternal critical pressure (1st stage labour)					
	150 mm.Hg −		200 mm.Hg		250 mm.Hg +	
mm.Hg	under 24 hours	24 hours+	under 24 hours	24 hours+	under 24 hours	24 hours+
50	2	2	6	1	4	—
100	5	6	3	2	3	2
150	2	3	4	—	1	—
100	—	—	1	1	1	—

TABLE X

Mat. Cr. Press.	Rises			Falls			No change		
Inf. Cr. Press.	R.	F.	NC.	R.	F.	NC.	R.	F.	NC.
Number	21	3	2	3	1	—	16	5	2
Per cent	80·8	11·5	7·7	75·0	25·0	—	69·5	21·8	8·7

Key: R.=rise; F.=fall; NC.=no change.

CORRELATION BETWEEN INFANT AND MATERNAL CAPILLARY RESISTANCE

It remains now to see whether or not there is any correlation between the infant and the maternal capillary resistance. The mother's capillary resistance in terms of mm.Hg can be compared with that of the infant. Experience during research reported by Walker and Balf (1954) has shown that the infant's initial capillary resistance when tested within 24 hours of birth can only be considered high if the test is positive at 150 mm.Hg or more. After 24 hours, it can be considered high if positive at 200 mm.Hg or more. The mothers' tests obtained early in labour were divided into the usual 3 groups, 150 mm.Hg or less, 200 mm.Hg, and 250 mm.Hg or more. The findings in 49 mothers and their infants are shown in Table IX.

Owing to lack of numbers any apparent trend in this analysis is not statistically significant.

The second method of assessing the correlation is to compare those mothers showing a definite rise or fall in resistance (100 mm.Hg or more) and those showing a change of 50 mm. Hg or less during the test period with the infants showing a rise, fall or no change in resistance.

It should be remembered that although 50 mm.Hg change in critical pressure is not considered of importance in the mother it is considered so in the infant. "No change" in the infant tests means literally no change in critical pressure over the test period. The results from 53 mothers and babies were thus tabulated.

Table X shows that the percentage of infants showing a rise is approximately the same no matter how the maternal capillaries are reacting to the effects of labour and the puerperium. This confirms the suggestion obtained from the previous analysis that there is no obsolute relationship between the infant and the maternal capillary resistance as tested by these methods. It is noted, however, that in most cases the resistance of mothers and infants rises from the time of birth till some time about or after the 8th day of the puerperium.

DISCUSSION

It has been clearly shown in the review of the literature on the subject of capillary resistance tests (Walker and Balf, 1954) that even the minor differences in technique considerably alter the results. The site tested, time of exposure, magnification and illumination of the area vary from one worker to another. It is unfortunately impossible, therefore, to compare the present

results, in terms of absolute values of mm.Hg pressure, with previous reports.

The explanation of the capillary resistance trends in mothers described above is difficult owing to the multiplicity of factors that might influence the resistance over the period of time during which the tests were performed. These factors include the effects of circulating sex hormones; the stress of labour and the possible adrenal response to this stress. It is notable that both the maternal (and the infants') capillary resistance rose in the majority of cases, from a definitely low value from the time of birth onwards, suggesting that there is a factor influencing both mother and baby prior to labour and possibly persisting into the puerperium; a factor at the outset common to maternal and foetal circulations.

(1) The first common factor that suggests itself is the level of circulating oestrogens.

In the mother, there is a high concentration of oestrogens present at term (Kerr, 1944; Venning, 1948) and this falls away fairly rapidly. The exact time at which this fall occurs is not known, but Venning (1948) showed the excretion of oestrogen products to continue right up till the onset of labour and thus cast doubt on the previous suggestion that the fall occurred prior to its commencemcnt. At the time when the concentration is at its height, the capillary resistance is lower than normal and as the concentration falls during labour and the puerperium the resistance rises. The rise observed is to levels far above normal and here the close inverse relationship is lost and a search for additional influences must be made. An interesting relevant fact, however, is that animal experiment has shown the administration of oestrogens to lower the resistance in dogs (Skelton *et al.*, 1946).

If capillary resistance changes are related to sex hormone levels in the blood, one might expect changes during the menstrual cycle. These have, in fact, been observed by Brewer (1938), and appropriate changes in oestrogen concentration were observed by Venning (1948) at mid-cycle though not immediately prior to menstrual flow. When the flow begins, however, the relationship is re-established. The exact timing of Brewer's tests is not known and it could be that many of them were performed when the oestrogens were at their height about the 20th day of the cycle and not during the following 8 days when the fall occurs. Loraine (1952) suggests that the oestrogen fall occurs about 4 days before the menses flow and if this were the case Brewer's findings would fit this hypothesis more accurately still.

Accurate estimation of day-to-day fluctuation in oestrogen excretion during the menstrual cycle is not available. The methods of assay used so far have been mainly biological and are inaccurate. Most workers agree, however, that a peak of total oestrogen excretion occurs about mid-cycle (12-15 days) and that there is a similar, though smaller, rise at about 21-24 days.

There seems to be, therefore, a relationship between the concentration of oestrogen and the capillary resistance. If this were so, it would have to be concluded that in the pregnant woman (and her infant) an increase in circulating oestrogen (probably Oestriol) caused a fall in resistance. In the light of this it is a little surprising that a closer correlation between the mothers' and infants' resistance was not demonstrated. However, it has been shown that the response to administered oestrogens in different individuals may vary (Swyer, 1950) and this may also be the case with the naturally occurring hormone.

Another observation of note is that of Bean, Cogswell, Dexter and Embick (1949) who observed vascular spiders and palmar erythema from the 2nd to 5th month of pregnancy onwards. This would suggest an abnormal capillary function during this period when the resistance tends to fall and the authors attribute the changes they observed to exposure to high concentrations of oestrogens over a considerable length of time. Hertz *et al.* (1949) administered very large doses of oestrogens to both males and females by intravenous injection and observed no vascular abnormalities whatever. This would suggest that it is not only the high concentration that is important, but that it must be present for a considerable time before the capillary changes are manifest.

That there is a wide range of "normal" (O'Hara and Hauck, 1936) has been confirmed by the present investigation and it is possible that this range is due to differing levels of circulating hormone. This might also explain the different

levels obtained on the same individual from time to time, bearing in mind that the male, as well as the female, is now considered to excrete oestrogens in the urine (Dingemanse, Laqueur and Muhlböck, 1938). This does not account, however, for the tests performed on the one individual varying on the two arms. It is not unreasonable to suggest that this is due to additional local differences in the tested areas. This hypothesis also falls short in the light of the known older age resistance trends, but it is quite possible that these hormones play an important rôle in the changes observed during the menstrual, reproductive and neonatal periods.

(2) In the mother the active and prolonged effect of labour, and to a lesser extent the rigors of pregnancy constitute a severe body stress. These, in themselves, are not likely to alter capillary function other than possibly affecting local trauma but the body responses which these stimuli evoke may well do. The response of the adrenal gland is one which may have some bearing on this subject.

The evidence concerning adrenal medullary response to the stress of menstruation, pregnancy and labour is contradictory. At times when vasoconstriction is said to occur and the level of epinephrine in the blood is high (a time at which, experimentally, an increase in capillary resistance has been observed; Robson and Duthie, 1950) a fall in resistance occurs (Brewer, 1938). Burt (1949) found vaso-dilatation before labour which was maintained well into the puerperium and it seems unlikely that the resistance is related to capillary vasomotor function.

Probably much more important is the adrenal cortical response as it has been recently suggested that the adrenocorticotrophic hormone (ACTH) of the anterior pituitary gland has an effect on capillary resistance. Robson and Duthie (1950, 1952) found a marked increase in resistance when giving ACTH to patients with rheumatoid arthritis and idiopathic thrombocytopenic purpura. Only one other similar report could be found, that of Bethell, Miller and Meyers (1951) who found a reversal of the Rumple-Leede test following ACTH therapy in cases of "hypersplenic syndrome". It is interesting to find that cortisone prevented an increase in capillary permeability in allergic reactions (Selye, 1949) and it may, therefore, have an effect on the resistance (Ambrose and De Eds, 1947). No other published work could be found concerning the relationship between ACTH and cortisone, and the capillary resistance. It is quite possible, however, that the maternal (and infant) adrenal response to stress during labour is related to their capillary resistance.

What evidence is there in the mother of adrenocortical activity and how do the capillaries behave in relation to this activity? Venning (1948) using a bioassay method has discovered two peaks of corticoid excretion during pregnancy, one in the first and one in the third trimester. Tobian (1949) using a more accurate modified Loewenstein chemical assay confirms this finding and states that the maternal adrenal cortex is hypertrophied in late pregnancy. Canton, Reid and Roby (1951) state that hypertrophy occurs in the pituitary and adrenal glands in "some" pregnancies. There is, however, a fall of corticoid output in the 10 weeks prior to labour (Venning, 1948) and some time during this period a slight but significant drop in capillary resistance occurs.

Additional evidence of corticoid activity during pregnancy is found in the peripheral blood picture. Hills, Forsham and Finch (1948) showed that ACTH produced, in the presence of a normal adrenal gland, leucocytosis, lymphopenia and eosinopenia. This is precisely what happens during pregnancy and to a greater extent during labour (Rath *et al.*, 1950; Davis and Hulit, 1949).

It has been mentioned that the capillary resistance was found to fall before term when corticoid excretion was falling and when there is strong evidence to suggest high adrenal cortical activity during labour there is a marked rise in resistance. The rise continues well into the puerperium which coincides with the findings of Rath *et al.* (1950) who consider the cortical effects to be evident for 2 to 4 weeks.

It is difficult to know just where operation and its effect on resistance fit into the picture. Tissue damage, blood loss, and a "stress" effect are common to both labour and operation. That a rise in resistance does occur in both is beyond doubt (Robson, 1949), but again one may have to look to the adrenal gland for the mechanism.

It is interesting to find that during elective Caesarean section (presumably prior to labour) similar adrenal responses to those found in normal labour were observed (Davis and Hulit, 1949).

The close relationship described above is not altogether upheld when the facts concerning the menstrual cycle are examined.

The findings of Brewer (1938) and Davis and Hulit (1949) do not fulfil the requirements. This may be due to the difficulty of knowing the exact timing of both resistance tests and hormone changes and to the fact that more accurate chemical assay of adrenal corticoids is casting doubt on past beliefs.

Once again, as with the oestrogens, a close but not complete correlation has been shown. In the general picture of stress reaction both cortex and medulla are said to play a part (Selye, 1950). The medulla and cortex need not react to the same degree when exposed to the same stimulus, but it is a little surprising to find peripheral vasodilatation when the stress is at its height during late pregnancy, labour and early puerperium. In view of this incomplete relationship, it is unlikely that the capillary resistance is influenced by adrenal gland secretions alone. Venning (1946) has observed an apparent stimulation of the adrenal gland on administering oestrogens and suggests that the high level of corticoid excretion in the third trimester of pregnancy may be "oestrogenic" in origin. The very low oestrogen level in the first trimester could not, however, be responsible for the less dramatic rise in corticoid excretion at that time.

(3) The effects of Vitamin P on the capillary resistance of the pregnant mother have been studied, but unfortunately no definite conclusions have been reached. The fact that the resistance is not related to Vitamin C concentrations alone is accepted fairly widely (Munro *et al.*, 1947; Scarborough and Bacharach, 1949) though there is still some doubt about the other factor related to resistance, "substance P" being a vitamin. The two substances are intimately linked, however, and it is of great interest that Vitamin C is also closely associated with the adrenal cortex. That capillary resistance is altered when there is deficiency of Vitamin C and Vitamin P is beyond doubt, but it is not known whether the deficiency has a direct effect on the capillary wall or is operative via the adrenal hormones. That Vitamin C and adrenal cortical activity are closely linked is now widely accepted (Giroud *et al.*, 1940; Ragan, 1951; Jailer, 1951; Levine *et al.*, 1951), definite changes in blood and urine Vitamin C and urinary corticoids being observed on administration of ACTH and cortisone. There is still difference of opinion about the need of Vitamin C in adrenal corticoid synthesis.

ACTH and cortisone appear to ameliorate scurvy symptoms (Ragan, 1951; Schaffenburg *et al.*, 1950), but the latter is not apparently able to replace Vitamin C entirely in the treatment of scurvy. It does, however, counter the increased activity found in this condition in guinea-pigs (Clayton and Prunty, 1951). Although the exact relationship is by no means clear, these authors, in the light of a comprehensive review of the literature and in the light of their own work, conclude that the balance of evidence is in favour of there being increased adrenal cortical activity in scurvy. This suggests that the adrenal gland responds to the Vitamin C deficiency state by secreting excess hormone and thus attempts, among other things, to restore the low capillary resistance to normal.

There is some evidence to suggest that the seasonal variations in resistance are related to fluctuation in the intake of Vitamins C and P containing foods. It might be expected that during the winter and spring months, when fruit and vegetables are scarce and expensive, a deficiency might be reflected in the state of the capillaries (Gothlin, 1931). There is, however, some slight disagreement in the literature as to the actual months at which the resistance is at its lowest. The seasonal availability of fruit and vegetables varies from one country to the other and if the seasonal trend were related to their intake one might expect reports from various parts of the world to differ.

In discussing the subject of seasonal variations a detailed report by Biskind (1946) is worthy of note. There appears to be ample experimental evidence to suggest that oestrogens are inactivated by the liver and that undernutrition, particularly involving the Vitamin B group, causes sufficient liver damage to depress this process of

inactivation. Oestrogens normally inactivated by the liver therefore accumulate in the body and could cause an alteration in the capillary resistance. This undernutrition possibly seasonal in time might well include lack of Vitamin C, but this idea once more indicates how closely related all these factors are to capillary resistance. No final conclusion on these points can, however, be reached.

(4) There is one further factor worthy of consideration and that is histamine. The first point of importance of the effects of histamine is the observation by Robson and Duthie (1950) that intravenous infusion of histamine caused a definite fall in capillary resistance and 2 other workers were quoted as having obtained similar results.

Kapeller-Adler (1953) tested both mothers and infants and found approximately the same amount of histamine in the maternal and cord plasmas and a higher red blood cell content in the cord blood at the time of delivery. More important, however, was her finding that while the mothers' plasma contained considerable quantities of histaminase, none could be detected in the cord plasma. This is similar to the findings of Swanberg (1949) who showed the "histaminolytic action" of umbilical blood to be 1/100th to 1/1,000th of the maternal blood level, thus approximating to those found in adult males and non-pregnant females.

The same author also observed a very high concentration of histaminase in the liquor amnii the full significance of which remains obscure.

In the mother during uncomplicated pregnancy the reaction to histamine injection is abnormal (Roberts *et al.*, 1944) and it has been shown that maternal blood contains considerably more histaminase than the non-pregnant subject (Kapeller-Adler, 1951). This is apparently produced by the decidual portion of the placenta (Anrep, Barsoum and Ibrahim, 1947; Swanberg, 1949) and a peak occurs about the 22nd-26th week there being a gradual fall till early pregnancy levels are reached about the 4th day of the puerperium. This does not entirely agree with the results obtained by Anrep *et al.* (1947) who found the maximum concentration at term, but there is little doubt that histaminolytic substances are present at this time in considerable concentration.

At term both histaminase and histamine are detected in maternal plasma, the former in considerable quantity. It is perhaps less likely therefore that the capillary function in the mother is affected by this histamine, but its presence coincides with the prenatal fall in resistance. As labour and puerperium progress the histaminase concentration falls and theoretically the histamine (if still present) should be free to produce a further fall in resistance. At this time, however, a rise in resistance occurs.

The exact timing of the disappearance of the histaminase is still rather in doubt (Kapeller-Adler, 1951; Anrep *et al.*, 1947), but it can be said that this histaminase returns to non-pregnancy levels as the capillary resistance is rising. In view of these facts it is possible that histamine plays at least a small part in the control of capillary resistance in the mother.

Conclusion

It can be seen that it is impossible to implicate any one of the above factors as being responsible for the changes in capillary resistance in mothers. Seasonal changes seen in children and adults are possibly related to under-nutrition, with particular regard to Vitamins C and P and to liver dysfunction. It is quite likely that a number of factors work together to effect the other changes detailed above and that the most notable are probably the circulating oestrogens, the adrenal cortical hormones and histamine in that order.

Summary

(1) Normal adult female variation and technique of testing resistance are discussed.

(2) There is a significant fall in resistance prior to term and a significant rise in resistance during labour and the puerperium is demonstrated, the final resistance being significantly higher than the non-pregnant control group. This demonstrates an "over-compensation" effect following the onset of parturition.

(3) The minor complications of pregnancy encountered did not appear to alter these trends.

(4) The resistance changes observed in pregnant women on Vitamin P therapy were not significantly different from the non-treated cases.

(5) There appears to be no relationship between the capillary resistance and blood loss during parturition.

(6) Obstetrical operative procedure did not alter the resistance trends to any detectable degree. Maternal capillary resistance does not appear to be related to the period of gestation at which labour occurs or to the duration of labour itself.

(7) There is apparently no relationship between the infant and the maternal capillary resistance, but in most cases the maternal and infant resistance rises from the time of birth till about or after the 8th day of the puerperium.

(8) No single factor could be considered as the influence initiating the capillary resistance changes observed. It was concluded that the resistance was probably controlled by a balance of several factors, notably oestrogens, adrenal cortical hormones, histamine and vitamin deficiency.

We wish to express our thanks to the Obstetricians and Paediatricians of the Simpson Memorial Maternity Pavilion and the Western General Hospital, Edinburgh, who kindly granted permission to examine the mothers and infants in their charge; to the Matrons, Sisters and Nursing Staffs of the hospitals for their very helpful co-operation; and particularly to those nurses who volunteered to act as control cases.

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THE EFFECT OF CATION EXCHANGE RESINS IN THE TREATMENT OF PRE-ECLAMPTIC TOXAEMIA OF PREGNANCY

BY

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THE oedema of pre-eclamptic toxaemia of pregnancy is, like other forms of oedema, associated with retention of sodium as well as water. In recent years attempts have been made to control the oedema by controlling the sodium intake of the patient, in the hope of improving the patient's general condition and preventing the onset of eclampsia (see Dieckmann, 1952, for review of subject).

Willson (1949) and Willson and Penman (1950) have shown that a diet low in sodium (less than 2 g. of salt) will reduce the amount of oedema in patients who have shown an excessive weight gain in pregnancy due to fluid retention, but they found that this treatment, which was slow and produced only a moderate loss of body fluids, was of little value in the fully developed pre-eclamptic state. Penman (1951) used cation exchange resins in the management of the fluid retention of pregnancy and found that they permitted the ingestion of up to 2-3 g. of salt per day and yet still mobilized the excessive fluid present in the tissues.

Penman (1952) has treated a series of cases of excessive fluid retention and mild cases of toxaemia of pregnancy as out-patients with such a resin. He has found it to be effective in controlling fluid retention and quite safe in doses of 45 g. a day.

Carey (1952) used these resins in the treatment of fully developed pre-eclamptic toxaemia and found that a rapid weight loss occurred with the mobilization of tissue fluid, so that he maintained the pregnancy for a longer period than he would otherwise have done.

There are, of course, dangers to be considered in any line of treatment in which pregnancy is continued under these circumstances. For the mother there is the possibility of producing permanent vascular or renal damage. For the child there is the risk of foetal death *in utero* or post-partum as a result of placental insufficiency.

The possibility of permanent vascular or renal damage to the mother resulting from the pre-eclamptic state is not yet definitely settled. Dieckmann, Smitter and Rynkiewicz (1952) have recently decided in favour of the view that no permanent damage results from a true pre-eclampsia; but a certain diagnosis is very difficult at the time and can often best be made only in retrospect, so that even if we hold this view we may still have some cause for anxiety from prolonging the pregnancy.

The danger of foetal asphyxia from placental insufficiency naturally increases the longer that the foetus is *in utero*. A difficult problem therefore arises if the pre-eclamptic state develops when the baby is so small that its chance of survival is slender. It is in these cases that it may be worth while to try to prolong the pregnancy, if only for a few weeks, until the child is thought to have a better chance of survival.

Such cases are not uncommon and it was therefore decided to treat with a cation exchange

resin a series of cases most of whom had severe pre-eclamptic toxaemia. In all cases Resodec (Smith, Kline and French) was used, a cross-linked polyacrylic polycarboxylic cation exchange resin of which 77 per cent is combined with ammonia and 23 per cent with potassium. The usual dose was 30 g. 3 times a day, reduced to 15 g. 3 times a day after about 3 days.

Such resins behave as weak insoluble acids which readily combine with bases such as sodium, potassium, calcium and ammonia. If given in the acid form (combined with hydrogen ion) they may irritate owing to their acidity and it is therefore usual to give them combined with ammonia. In the intestines the ammonium ion is to a large extent exchanged for the ions of sodium, potassium, calcium, etc. which are bound to the resin and excreted in the faeces. It is clear that such resins will remove potassium and calcium (and presumably magnesium) as well as sodium, the amount being in direct proportion to the percentage of each present. It has been found in short term experiments at least that potassium loss may be important. This loss is much reduced by giving 23 per cent of the resin in the form of potassium compound, while the rest is combined with ammonia.

It should be noted that the ammonium resins convert salts of sodium, potassium, etc. into salts of ammonia, which are absorbed into the body. There the ammonia is converted into urea and the excess of acid radicles which remain produces an acidosis. It is, therefore, found that the cation exchange resins, whether in the hydrogen or ammonium form, produce an acidosis in the same way as does the ingestion of hydrochloric acid or ammonium chloride.

There are, then, two separate ways in which such a resin may promote the removal of body fluid. Firstly, by interfering with sodium absorption from the intestine, the resin may produce a sodium depletion and the kidneys will then excrete water in an attempt to keep the plasma sodium concentration normal. Secondly, by producing an acidosis, the resin stimulates the kidney to excrete the excess of acid radicles (mainly chloride). At first this increase of acid radicles in the urine is neutralized by sodium and potassium, and this renal loss of sodium helps to reduce the volume of body fluid. The kidney, however, soon produces ammonia in amounts sufficient to combine with nearly all the excess acids; thereafter the renal loss of sodium falls and the acidosis has little further diuretic effect.

Hence in the diuresis which follows resin administration the urine sodium concentration is high at first but then quickly falls to low levels as the acidotic effect falls away and the effect of low sodium absorption comes to predominate.

When patients were treated with resin a regular check was kept on the plasma levels of sodium, potassium, chloride and bicarbonate (as carbon dioxide capacity) in order to watch for serious acidosis or depletion of base. Normal plasma levels are considered to be sodium 310-330 mg./100 ml. (140±5 m. Eq./litre); potassium 14-20 mg./100 ml. (4·3±0·7 m. Eq./litre); chloride (as sodium chloride) 560-620 mg./100 ml. (100±5 m. Eq./litre); carbon dioxide capacity 50-70 vols. per cent (26±4 m. Eq./litre). In 2 cases the levels of sodium and potassium in urine and faeces were followed. After delivery the baby's plasma sodium and potassium levels were checked in 2 cases.

To avoid attributing to the resin effects due to other forms of treatment an attempt was made to stabilize all patients on a routine treatment first, and whenever possible the use of resin was delayed until it was considered that the maximal effect had been gained from this treatment. Accordingly all patients were treated in hospital, and given complete bed rest with sedation and a diet containing only 0·8 g. sodium (2 g. salt) daily. The blood-pressure was recorded 4-hourly while the patient was awake. Measurements were made of the patient's drinks and urine output and of the approximate urine protein concentration by Esbach's urinometer. A full fluid balance was not attempted but the patient was weighed every day to indicate significant changes in body fluids. In the figures the patient's intake of drinks and output of urine are charted by Albright's method, intake being charted downwards and output upwards from the intake level; this shows output relative to intake but does not give a true balance because it ignores such factors as fluid intake in food and output by evaporation and in faeces. It is, moreover, doubtful whether the measurements of drinks and urine were accurate enough for a complete balance.

The urinary protein is expressed as output in grams per 24 hours, not as urinary concentration which may be expected to fall whenever diuresis occurs.

CASE 1. J.R. (see Fig. 1).

This patient, aged 27 years, was expecting her first baby and was attending the antenatal clinic. She had an uneventful pregnancy until the 34th week, when she was found to have a blood-pressure of 165/100, marked oedema and a heavy cloud of albuminuria; she had gained 8 pounds in weight over the previous 3 weeks.

She was immediately admitted, confined to bed, sedated with paraldehyde and phenobarbitone and put on a diet containing 0·8 g. sodium daily. On admission the blood urea was 27 mg./100 ml. and a catheter specimen of urine showed no casts, but she was excreting approximately 5 to 7 g. of protein daily in the urine. She continued to gain weight slightly and her blood-pressure remained about the same. By this time she had reached the 35th week of gestation but as the foetus seemed very small it was decided to start a course of the resin. Twenty-four hours after starting the resin she had a well marked diuresis and lost 14 pounds in weight over the next 4 days; urinary protein output became less and the blood-pressure tended to fall. At the same time she developed an acidosis and sodium depletion, the plasma carbon dioxide capacity falling from 58 to 35 volumes per cent (26 to 15·5 m. Eq./litre) and sodium from 311 to 299 mg./100 ml. (135 to 130 m. Eq./litre). The serum calcium was 9·4 mg./100 ml. The urinary excretion of both sodium and potassium rose at first with the acidosis and then gradually fell as more sodium was being eliminated in the faeces—the faecal sodium output averaging over 0·8 g./day during this period. The plasma potassium fell slightly from 18·9 to 17·8 mg./100 ml. (4·8 to 4·6 m. Eq./litre).

In view of the great improvement in her condition, the acidosis and her dislike of the resin, the course was stopped. However, after 3 days her weight had increased by 5 pounds and there was an increased protein loss in the urine. As her plasma sodium had returned to 308 mg. per cent (134 m. Eq./litre) and her carbon dioxide capacity to 47 vols. per cent (21 m. Eq./litre), a second course of the resin was started, giving only half the original dosage. This did not have such a marked effect as the first course but there was a slight loss of weight and the situation was held in check. After 6 days there was again an acidosis and nausea: plasma sodium 300 mg./100 ml. (131 m. Eq./litre) and the carbon dioxide capacity 37 vols. per cent (16·5 m. Eq./litre) and it was again decided to give her a rest. The faecal sodium output at this stage was about 0·65 g. per day.

During the next 4 days she gained 5 pounds in weight but by this time she had reached the 38th week and it was felt that the baby was large enough. Accordingly a surgical induction was performed and she went into labour at once. She had a first stage of 6 hours and a second stage of 2 hours, followed by a forceps delivery of a living child weighing 5 pounds 5 ounces.

The baby did well and was discharged home well above its birth weight. The mother's blood-pressure fell to 120/80 on discharge and the urine was clear. At 3 months and at 10 months after delivery both the blood-pressure and urine were normal.

COMMENT

The resin tided this patient over for 3 weeks until the 38th week, when the baby weighed 5 pounds 5 ounces. Without the resin it would have been decided to terminate the pregnancy earlier and a live baby might not have been obtained. The mother seems to have sustained no permanent vascular or renal damage as a result of prolonging her pregnancy. It is interesting to note the enormous fluid loss that occurred with the resin, whereas a low sodium diet by itself had had no effect. The fluid loss was most marked at the start of the first course. On the second course, with a lower dosage, there was less diuresis but ultimately a similar degree of acidosis was obtained. Apart from the lower dosage, other factors contributing to the smaller effect of the second course may have been the lesser degree of oedema present at the start, and, secondly, a higher initial level of ammonia synthesis by the kidney, thus limiting renal loss of sodium. The plasma potassium level fell only slightly and a single serum calcium at the end of the first course was within the normal range.

CASE 2. I.M.S. (see Fig. 2).

This patient, aged 23 years, was expecting her first baby and attended her own doctor. Her pregnancy was uneventful until the 32nd week, when she was found to have a blood-pressure of 140/90, a heavy cloud of albumen in the urine and some oedema.

She was immediately admitted to hospital, where she was put on complete bed rest, sedated with phenobarbitone and nembutal and given a diet containing 0·8 g. sodium daily. Her blood-pressure was very variable and showed no definite trend up or down, and her weight remained steady. She was, however, excreting up to about 13 g. protein in the urine in 24 hours. Clinically the foetus was very small.

After 4 days with no improvement a course of resin was started. There was a distinct diuresis after 24 hours and she lost 7 pounds in weight in the next 5 days. During this time the faecal sodium output was between 0·5 and 0·6 g./day. After 7 days on the resin her weight was steady, her plasma sodium had fallen from 302 to 287 mg./100 ml. (131 to 125 m. Eq./litre) and plasma carbon dioxide capacity from 58 to 47 vols. per cent (25 to 21 m. Eq./litre). As she was becoming very nauseated

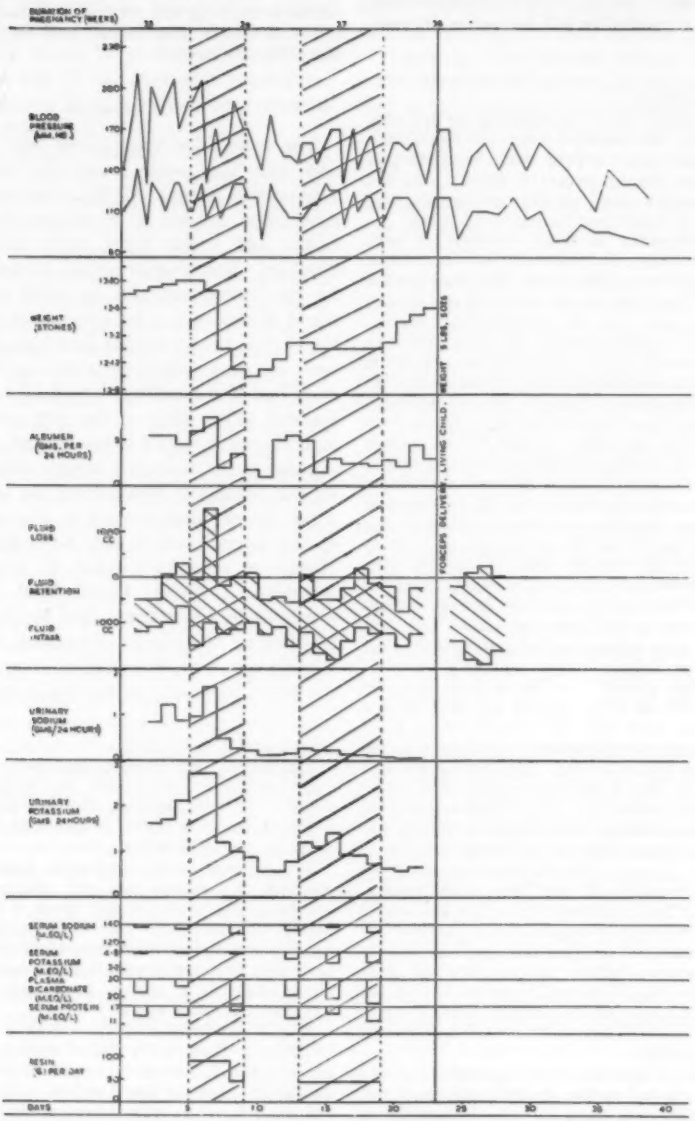

FIG. 1. Case 1. (J.R.)

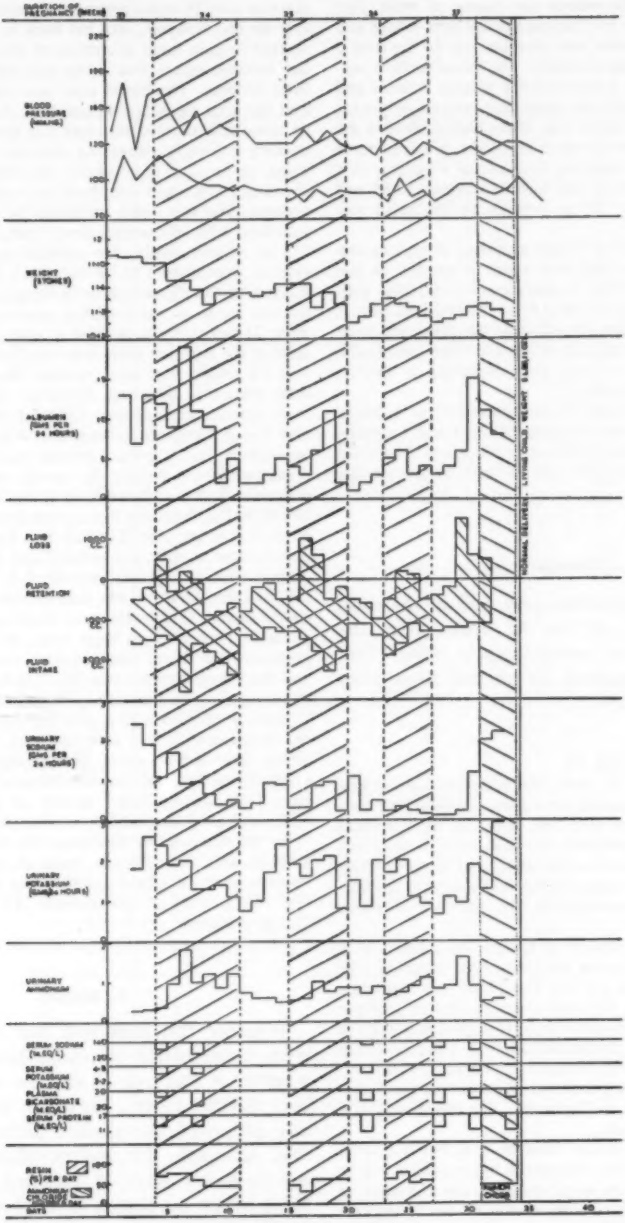

FIG. 2. Case 2. (I.M.S.)

it was decided to discontinue the course of resin. Her weight gradually rose by 3 pounds in the next 4 days and a further course of resin was then started. In the next 5 days she lost 6 pounds in weight. The faecal sodium output rose to over 1·0 g./day and the plasma sodium and carbon dioxide capacity fell again. She became intolerant of the resin and the course was discontinued. Within the next 3 days she gained 4 pounds in weight. A third course of resin was started, resulting in a loss of 4 pounds in 4 days. The blood-pressure was now averaging 130/90 and she was losing from 2-3 g. protein in the urine per 24 hours.

After a rest period of 5 days a course of ammonium chloride (45 gr. per day) was tried. However, as the patient started to have a spontaneous diuresis with increased urinary sodium output on the previous day, it was impossible to assess the effect of the drug. She went into labour on the third day of this treatment and had a normal delivery of a living child weighing 5 pounds 11 ounces at the 38th week.

On discharge the mother's blood-pressure had fallen to 110/80 and there was no albuminuria. At 3 and 9 months after delivery the blood-pressure was normal. The child did very well and was well over its birth weight on discharge.

Comment

This patient responded very well to the resin and was carried on for 4½ weeks after the appearance of the pre-eclamptic state. Her blood-pressure returned to normal soon after delivery.

Case 3. M.A.G. (see Fig. 3).

This patient, aged 36 years, was pregnant for the first time. She had been married for 1 year when she first consulted her own doctor and was found to be 4 months pregnant. Her blood-pressure was then 160/110 and there was a trace of albumen in the urine. Her doctor subsequently sent her for consultation and she was immediately admitted for investigation. She was then 21 weeks pregnant.

On admission a trace of albumen was present in a catheter specimen of urine but there were no casts. The blood urea was 18 mg. per cent and 20 mg. per cent when repeated 1 week later. The urea clearance was only 36 per cent but she concentrated her urine to a specific gravity of 1,023 and to a urea concentration of 2·1 per cent. An intravenous pyelogram showed both kidneys to be normal in size, shape and position and there was good concentration of the dye in 5 minutes. The blood uric acid was 3·4 mg. per 100 ml.

It was difficult to decide whether this was a case of chronic nephritis or one of essential hypertension, but as the patient would not even consider the question of terminating her pregnancy, the treatment was in any case conservative. Her condition seemed fairly stable and as she was only 25 weeks pregnant she was sent home to rest. Her doctor, however, sent her back in 10 days as she had started to pass large quantities of albumen in the urine, her blood-pressure was rising and she had developed a little oedema. The blood urea was then 30 mg./100 ml. and her urea clearance 46 per cent. A catheter specimen of urine still showed no casts but she was found to be passing gradually increasing amounts of protein in the urine, up to 12 g. in 24 hours. Her weight had remained constant for 4 weeks and there was very little evidence of oedema. She was again stabilized by complete bed rest, sedation with phenobarbitone and a diet containing 0·8 g. sodium daily. On ophthalmoscopy the retinal arteries were shown to be narrowed. She was now considered by the physicians to be a case of essential hypertension with a super-added pre-eclamptic toxaemia. After 2½ weeks it was decided to give a course of resin in spite of the fact that there was very little clinical oedema, that the weight had been constant for 4 weeks and that little effect was expected. However, the patient had an early diuresis, passing over 5,000 ml. of urine in 24 hours and losing 8 pounds in weight in 4 days. There was an appreciable fall in urinary protein output and the blood-pressure fell very slightly. By the 4th day of treatment her plasma sodium had fallen from 319 to 307 mg./100ml. (139 to 134 m. Eq./litre) and her carbon dioxide capacity from 60 to 37 vols. per cent (27 to 16·5 m. Eq./litre). On the 5th day the dose of resin was reduced and by the 10th day the carbon dioxide capacity recovered to 57 vols. per cent (25·5 m. Eq./litre) but the sodium remained low. After a course lasting 12 days the resin was stopped to relieve the patient's nausea. Two days later, at the 31st week of gestation, the foetal heart became very difficult to hear and the movements became less. The baby, however, was of so small a size that it was thought to have almost no chance of survival and it was decided not to terminate the pregnancy. It was soon obvious, however, that the foetus had died *in utero*. The mother's blood-pressure gradually settled and the albuminuria became less. Ten days later she delivered herself of a very macerated hydrocephalic foetus and a necrotic placenta.

By the time of her discharge the blood-pressure was 140/100 and there was a trace of albuminuria. Nine months later the blood-pressure was 155/110 and there was still a trace of albuminuria. The blood urea was 22 mg. per cent.

Comment

Whether this case was one of hypertension with super-added pre-eclamptic toxaemia or whether it was one of chronic nephritis is still very difficult to say. However, the resin materially improved the clinical picture very rapidly and although the hydrocephalic foetus died within a few days of finishing the treatment, there seems no reason to believe that the resin itself contributed to the foetal death.

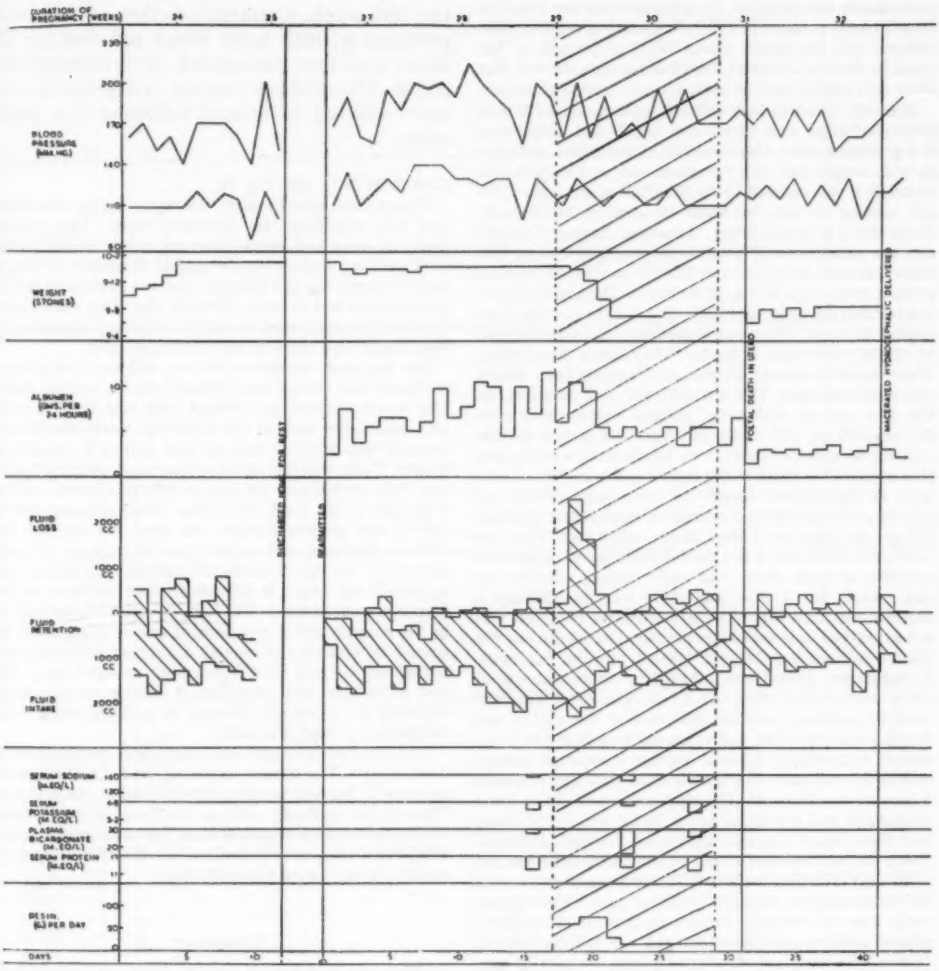

FIG. 3. Case 3. (M.A.G.)

CASE 4. E.G.M.J. (see Fig. 4).

This patient, aged 25 years, was expecting her first baby. Antenatal care had been undertaken by her own doctor, who said that the blood-pressure and urine had been normal until the 29th week, when he sent her immediately into hospital. On admission she was found to have a blood-pressure of 160/100. There was gross clinical oedema and she passed about 19 g. of protein in her urine in the first 24 hours. Ophthalmoscopy showed that there was some degree of narrowing of the retinal vessels.

She was rested in bed, sedated with paraldehyde and phenobarbitone and given the usual diet containing 0·8 g. sodium daily. Her condition deteriorated, with rise in both weight and blood-pressure and, as the baby was so small, it was decided to try the effect of the resin without waiting as long as usual to stabilize beforehand. There was a dramatic effect. A marked diuresis occurred and the patient lost 10 pounds in weight in 4 days. The blood-pressure dropped from 180/120 to 150/105, and the protein output fell to 3 g. in 24 hours. The patient could not tolerate the resin for longer than 6 days and was then given 4 days rest. There was immediate fluid retention and an increase in weight. A further 5-day course was started, which again produced diuresis and lowered both weight and blood-pressure. This was followed by 2 days rest, on the 2nd day of which the plasma sodium was only 287 mg./100 ml. (125 m. Eq./litre) and her carbon dioxide capacity 46 vols. per cent (21 m. Eq./litre). It was thought that some of the effect of the resin was due to the acidosis and, as the patient found the resin very difficult to tolerate, she was given a course of ammonium chloride (45 gr. per day) for 3 days after 2 days rest. This was ineffective and there was a further increase of weight and retention of fluid. Resin was again started, without any rest period, for 7 days and there was immediately a diuresis and some loss of weight, although the effect was not as marked as in the earlier courses. On the 6th day the plasma sodium was 282 mg./100 ml. (123 m. Eq./litre). A further rest period was followed by another course of resin, with similar effect. As it was now about the 36th week of pregnancy and the baby was of fair size, it was decided that the time had come to terminate the pregnancy. Accordingly a lower segment Caesarean section was performed and a living male child weighing 3 pounds 4 ounces was delivered. The child cried well, was a good colour and had a good air entry. It did well for 52 hours and then had 4 cyanotic attacks at 2-hourly intervals. These did not respond to any form of treatment and the child died after the last attack. The post-mortem showed no evidence of any bronchial obstruction but there was an early stage of broncho-pneumonia present. The baby's plasma sodium (cord blood sample) was 310 mg./100 ml. (135 m. Eq./litre) and its plasma potassium was 28 mg./100 ml. (7·2 m. Eq./litre). The sodium was normal and the potassium slightly raised and therefore the resin was not thought to have contributed to its death. On the same day the mother's plasma sodium was 310 mg./100 ml. (135 m. Eq./litre) and potassium 17·3 mg./100 ml.

Seven months later the mother's blood-pressure was 120/80 and there was no albuminuria.

COMMENT

The resin appeared to produce a remarkable clinical improvement and the pregnancy was therefore allowed to continue for 6 weeks until the 36th week. Caesarean section at this time produced a small baby, which did well for 52 hours and then succumbed to broncho-pneumonia. The mother's vascular system appears to have returned to normal following this pregnancy.

CASE 5. M.W.D. (see Fig. 5).

This patient, aged 24 years, was expecting her first baby and was attending the antenatal clinic. Her blood-pressure, urine and weight were all within normal limits until the 32nd week, when she gained 7½ pounds in weight and developed clinical oedema. She was advised to rest in bed at home and to take a low salt diet. Two weeks later the blood-pressure rose to 125/90, although albuminuria was absent, and she was admitted to hospital.

She was given complete bed rest, sedated with phenobarbitone and given a diet containing 0·8 g. sodium daily. The blood-pressure and weight both rose until a week after admission and, at the 36th-37th week, the blood-pressure was 170/120 and she had gained 8 pounds in weight. There was still no albuminuria. A course of resin was then started and she had a marked diuresis, losing 8 pounds in the week, while her blood-pressure fell to 130/90. Her plasma sodium was then 308 mg./100 ml. (134 m. Eq./litre) and carbon dioxide capacity 37 vols. per cent (17 m. Eq./litre). By this time she was feeling well in herself but found it difficult to take the resin so the course was terminated. The baby by this time seemed to be big enough and it was decided that nothing could be gained by waiting any longer. A surgical induction was performed and she went into labour straight away. She had a 10-hour first stage and a 2-hour second stage, followed by a normal delivery of a living male child weighing 6 pounds 7 ounces.

The child did well and was discharged home above its birth weight. The mother, however, had a rise of blood-pressure in the puerperium up to 180/140 on the fifth day. Then it fell gradually and on discharge it was 140/90. When she was seen at the 6th week the blood-pressure was 120/80 and the urine contained no albumen. The same condition was found 6 months later.

COMMENT

This patient could well have been induced at the 36th-37th week instead of using the resin. Its use, however, produced such a marked clinical improvement that when she did go into labour she was very much fitter. The baby was of good size and caused no anxiety. This case shows again the effect of the resin in producing a fluid

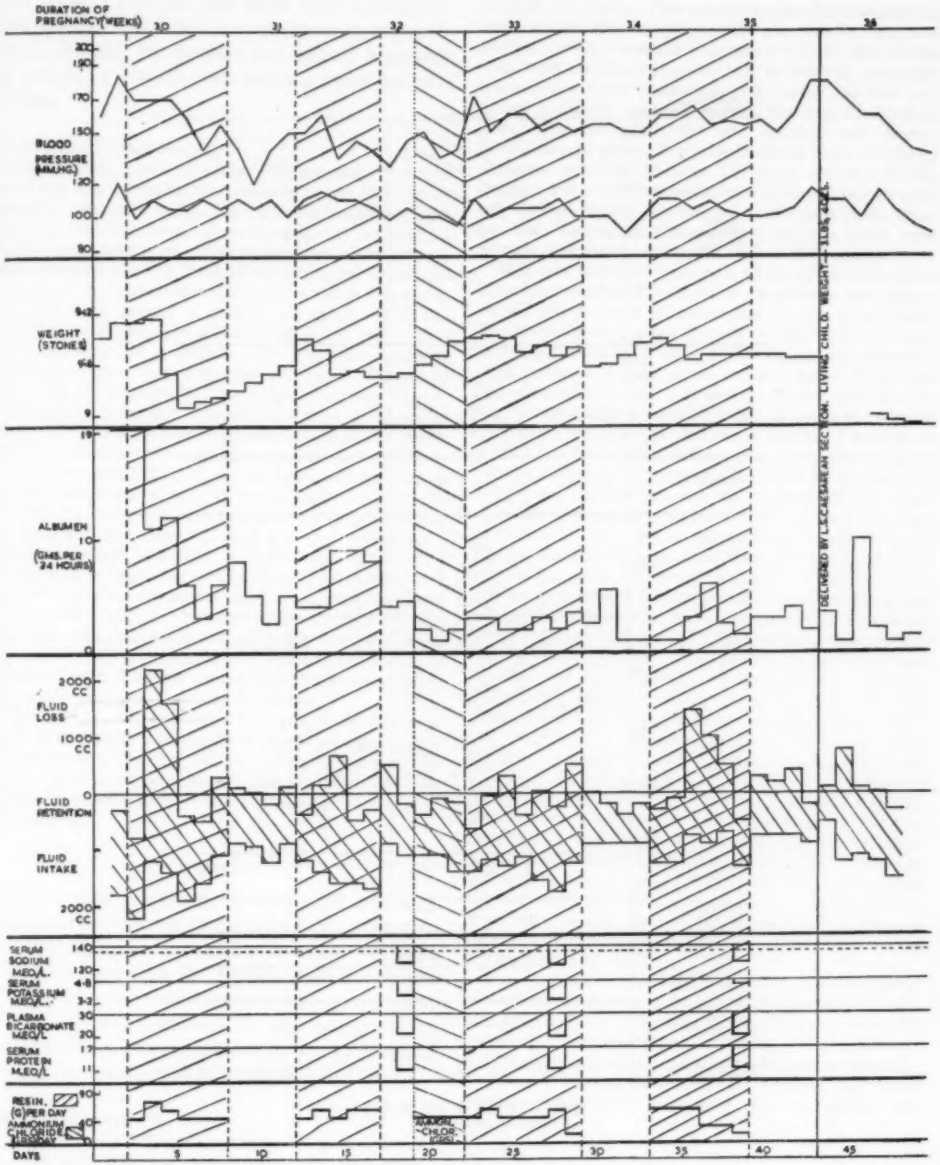

FIG. 4. Case 4. (E.G.M.J.)

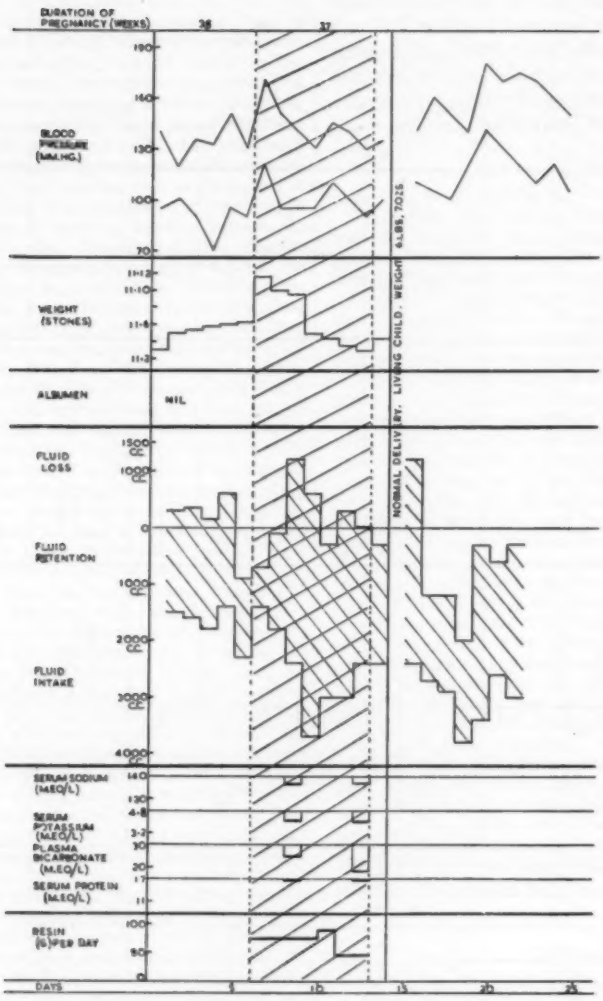

FIG. 5. Case 5. (M.W.D.)

loss when a low salt diet alone over a considerable period had failed to produce any improvement. Indeed, the patient had gained 8 pounds in weight in 1 week even under a strict hospital regime.

CASE 6. D.B.C. (see Fig. 6).

This patient, aged 22 years, was expecting her first baby and was attending the antenatal clinic. Her blood-pressure, urine and weight were all within normal limits until the 34th-35th week, when she gained 6 pounds in 2 weeks and developed clinical oedema. Her blood-pressure rose to 130/85. She was advised to rest in bed and take a low salt diet at home. She improved at first but in the 2nd week gained 3 pounds in weight. She was admitted to hospital and given complete bed rest, with a diet containing 0·8 g. sodium daily. Her blood-pressure fluctuated slightly but never rose very much. There was never any albuminuria but her weight continued to rise, increasing by a further 5 pounds in 8 days. A course of resin was then started and she lost 7 pounds in 3 days, while her plasma carbon dioxide capacity fell from 60 to 48 vols. per cent (27 to 22 m. Eq./litre) and her plasma sodium remained steady at about 310 mg./100 ml. (134 ml. Eq./litre). She found great difficulty in tolerating the resin and was allowed 2 days rest, during which she gained 4 pounds in weight. A further course was then started and brought the weight down by 3 pounds in 3 days. By this time the patient was just past the 38th week and the baby was of good size. Accordingly a surgical induction was performed and she went into labour the next day. The first stage of labour lasted 6 hours and the second ¾ hour, followed by normal delivery of a living male child weighing 7 pounds 12 ounces.

The child did well and was discharged home almost up to its birth weight. The mother's blood-pressure rose in the puerperium, reaching the level of 145/100 on the 4th day. It then gradually settled and on discharge was 120/80. At the 6th week it was 120/80 and there was no albuminuria.

COMMENT

In this case the toxaemia was mild, the only important symptoms being the fluid retention and the increase in weight. In spite of strict hospital regime with low sodium diet, the weight continued to rise until the resin was given, when a rapid fall was obtained. It was interesting to note the rise of blood-pressure in the puerperium but this soon returned to normal.

CASE 7. D.E.T. (see Fig. 7).

This patient, aged 27 years, was expecting her first baby and was attending the antenatal clinic. Her blood-pressure, urine and weight were all within normal limits until the 31st week of the pregnancy, when she developed slight oedema of the ankles. She had gained 15 pounds since the beginning of the pregnancy but the increase had been steady. Her blood-pressure was 110/70. She was advised to rest at home and to take a low salt diet. At the 33rd week the blood-pressure rose to 180/110, and there was a heavy cloud of albumen in the urine. She had only gained a further pound in weight. She was admitted at once, given complete bed rest, sedated with phenobarbitone and given a 0·8 g. sodium diet daily. The baby appeared small for the dates. The blood urea was 20 mg. per cent and a catheter specimen of urine showed no casts but she was passing between 4-8 g. albumen in the urine per day. The serum albumen and globulin levels were normal. Her general condition showed little change.

As it was suspected that some of the effect of the resin in previous cases had been due to the acidosis, this patient started with a course of ammonium chloride 45 gr. daily. There was no noticeable diuresis but her blood-pressure and weight both fell a little. After 4 days she developed a toxic erythema and the course was terminated. There was little change in the next 5 days and resin was then started. There was at once a marked improvement in the clinical condition; she had a good diuresis and lost 5 pounds in weight in 3 days although there was no significant fall in plasma sodium or bicarbonate. She tolerated the resin for 5 days and was then given a rest. On the 3rd day, however, her blood-pressure rose to 180/120. She was now past the 37th week and in spite of the fact that the baby seemed small for its dates, it was thought to be big enough to stand a good chance of survival; it was therefore decided to terminate the pregnancy. A surgical induction was performed and the liquor was found to be heavily stained with meconium. This was interpreted as an indication of foetal distress although the foetal heart was regular. A lower segment Caesarean section was performed within an hour and a living male child weighing 3 pounds 14 ounces was delivered. Its condition was poor and in spite of an apparently clear trachea on laryngoscopy, it remained cyanosed and its breathing was laboured. It died 14 hours after birth. A post-mortem examination showed that the cause of death was asphyxia resulting from atelectasis. The air passages were completely clear and there was no congenital abnormality. There were pericardial and bilateral pleural effusions which were thought to be due to asphyxia resulting from the atelectasis. The baby's serum sodium and potassium levels were within normal limits. The placenta showed massive infarction which probably accounted for the foetal distress *in utero*.

The mother's blood-pressure did not return to normal at once. When she was discharged it was 140/80 and there was still a trace of albuminuria in a catheter specimen. At 6 weeks the blood-pressure was 160/80, at 10 weeks it was 150/90 and there was still a trace of albumen in the urine. At 5, 6 and 7 months after delivery, however, the blood-pressure was 130/80 and there was no longer any albuminuria.

COMMENT

This case illustrates the fact that a low sodium diet, either alone or combined with small doses

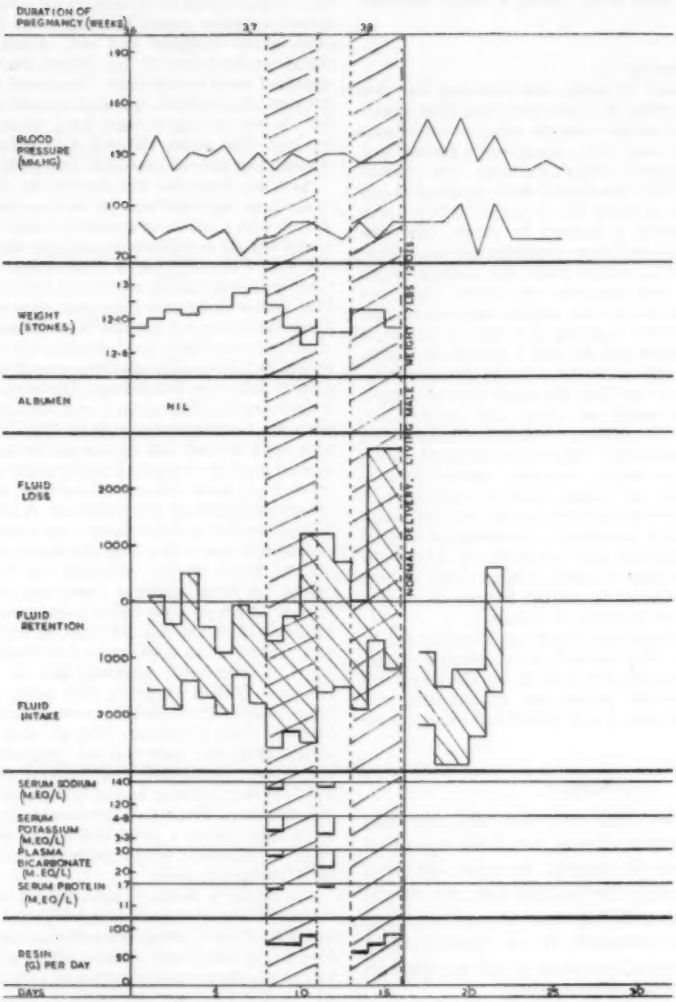

FIG. 6. Case 6. (D.B.C.)

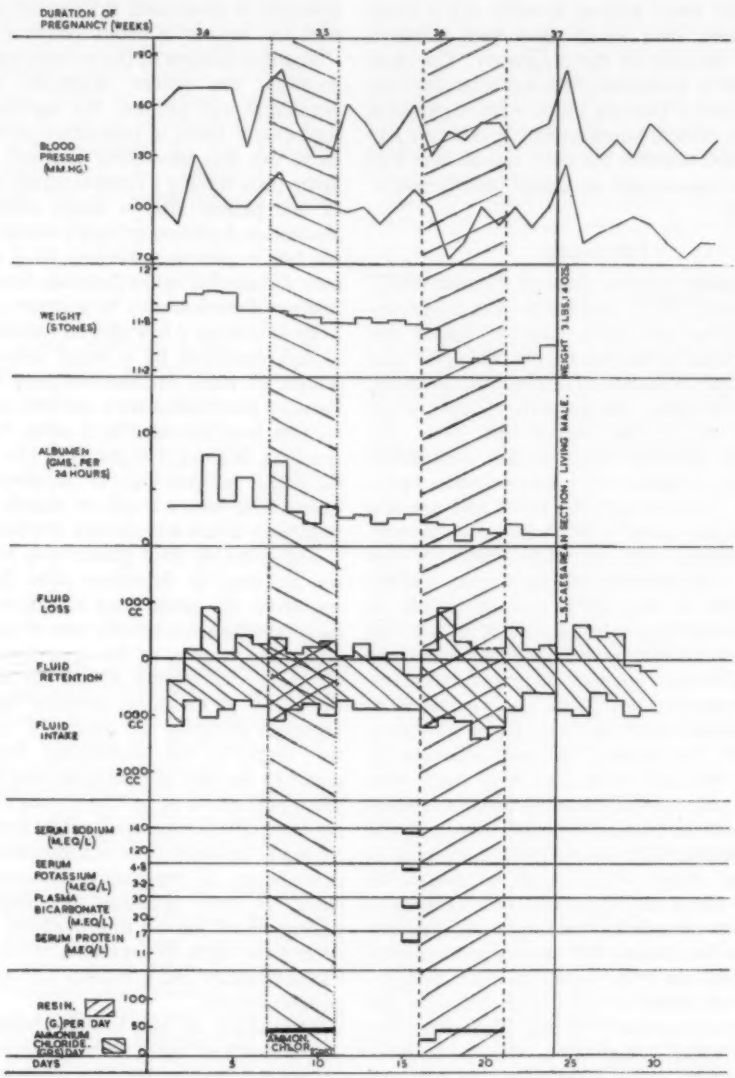

FIG. 7. Case 7. (D.E.T.)

of ammonium chloride, has little effect unless resin is given also. The massive placental infarction caused foetal distress *in utero* and a much smaller baby than would have been expected from the duration of the pregnancy. The child succumbed to atelectasis 14 hours after delivery. It is considered that the resins were responsible for a great clinical improvement in this case and it is doubted whether the baby would have had any better chance with an earlier termination of pregnancy.

Discussion

These results confirm those of Penman (1952) and of Carey (1952) and show that cation exchange resins are most effective agents for reversing fluid retention in pre-eclamptic toxaemia. They act mainly by diminishing intestinal sodium absorption and are only effective when combined with a low sodium diet. They also produce an acidosis which initially contributes to the loss of sodium by increased renal excretion. Fig. 1 shows how the initial and greatest diuresis is associated with an increased urinary sodium output (i.e. an early effect of the acidosis), while subsequently the urinary sodium output falls to low levels (i.e. the result of diminished intestinal absorption). It is true that ammonium chloride by itself had little effect but the dose given was too small: 45 gr. of ammonium chloride represents only 57 m. Eq., whereas 90 g. of resin represents about 90 m. Eq. of ammonia compound. The degree of acidosis produced by the resin was not severe and with more prolonged periods of administration would probably have diminished rather than increased, as the kidneys became fully adapted to the acidosis. If desired the acidotic effect could be reduced by giving an anion exchange resin simultaneously.

The effect on sodium absorption was excellent and in the first 2 cases the faecal sodium output rose to about the level of sodium in the diet, i.e. the resin converted a low-sodium diet into the equivalent of a sodium-free diet. As sodium-free diets are most unpalatable, this is a most valuable action, but it is unfortunately counterbalanced to a considerable extent by the unpalatability of the resin itself. Whatever the vehicle in which the resin was suspended, all patients found it unpleasant to take and soon complained of nausea, intestinal colic, etc. For this reason more than any other it was found desirable to administer it for short periods only, with rest periods of about 3 days in between.

Possible dangers to the patient, apart from the acidosis, are severe depletion of calcium, potassium and sodium. No significant calcium depletion is likely in such short periods of treatment but this possibility was not investigated apart from finding a normal serum calcium level in one patient after a single course of resin. Potassium depletion probably occurs, judging by the fall in plasma potassium level which, however, did not fall below the lower limit of normal. Sodium depletion may be a danger, for in some cases of oedema a low plasma sodium level is not always corrected by a water diuresis and the danger of water intoxication may be added to those of pre-eclampsia; a marked fall in plasma sodium level was seen in 2 cases, Nos. 2 and 4 reaching 287 mg./100 ml. (i.e. 125 and 123 m. Eq./litre) respectively. It is obviously most desirable to keep a check on plasma sodium and potassium levels when resins are being given.

The effect on fluid retention is clear but it is not so easy to determine how far the resin improved the underlying condition. Although fluid retention is normally one of the factors by which the severity of the condition is assessed, its exact relationship to the toxaemia is unknown. It is, therefore, possible that the resin, although reducing the degree of oedema, may not improve the underlying condition nor diminish the risk of eclampsia, and the fact that these patients took no harm from the permitted continuation of pregnancy might merely indicate a normal tendency to overcautiousness and early termination of pregnancy. However, in these cases the resin produced not only a loss of oedema fluid but an improvement in both the other main signs of toxaemia, i.e. a slight fall in blood-pressure and a distinct fall in the urinary protein output.

The effect on the protein output was not anticipated and hence no more accurate method of estimation than Esbach's albuminometer was used to estimate the albumen in the urine. The results obtained might therefore be due to a systematic error of this method, for instance, low protein concentrations resulting from increased

urinary output might read lower than their true values or the high concentrations obtained before diuresis might be reading too high. In either case a false impression of lowered protein secretion might be obtained when a diuresis occurred.

To test this possibility urines containing natural protein or urines to which plasma had been added were estimated by the Esbach's method, undiluted and also diluted one half and one quarter. The results are given in Table I

TABLE I

Undiluted	Diluted ½		Diluted ¼	
g./litre	g./litre	Per cent undiluted	g./litre	Per cent undiluted
12·8	5·8	45		
11·0	6·0	54	3·2	29
11·1	4·0	36	2·5	23
10·0	5·5	55	3·0	30
9·2	5·0	54	2·8	30
9·0	4·0	44	2·8	31
7·0	3·8	54	2·8	40
5·9	2·5	42	1·5	25
3·8	1·8	47	1·2	31
2·2	1·8	82	1·2	55
2·0	1·5	75	1·0	50
1·8	1·0	55	0·7	35

and show that there is no systematic error causing low concentrations of protein to read proportionately lower than high concentrations. It therefore seems that the fall in protein output found in these patients was genuine. It is therefore reasonable to suppose that there was a real improvement in the patient's condition as a whole which made it safer to allow the pregnancy to continue.

So far as is known the resin had no ill-effect on the foetus. However, in allowing any pre-eclamptic pregnancy to proceed there is always a danger of foetal death from placental insufficiency. Three babies were lost in this series. One was a hydrocephalic that died *in utero* at 31 weeks; the mother had hypertension with a severe super-added toxaemia. One baby weighed 3 pounds 4 ounces and was delivered at 36 weeks; it did well for 52 hours and then developed broncho-pneumonia and died. The other was delivered at 37-38 weeks, weighed 3 pounds 14 ounces and died after 14 hours from atelectasis. It is doubtful whether either of these babies would have been saved by earlier termination, as they both died of the hazards of prematurity.

There is no evidence in this small series that a prolongation of the pre-eclamptic state is likely to result in permanent vascular or renal damage, for in all cases the blood-pressure and urine returned to pre-pregnant levels within a few months of delivery.

It is considered that the cation exchange resin is the most effective agent yet in the control of excessive fluid retention in the pre-eclamptic state and that it also materially improves the overall clinical picture by producing a distinct improvement in renal function. It is felt that it has an important part to play in the treatment of this condition but its prolonged use should be restricted to those few cases where it is advisable, in the interests of the child, to carry the pregnancy on for a few more weeks.

SUMMARY

A cation exchange resin was used in the treatment of 7 cases of pre-eclamptic toxaemia of pregnancy and it is considered to have exerted a beneficial effect. The indications for its use and the dangers which may result are discussed.

We wish to thank Mr. H. L. Shepherd and Dr. Mabel Potter for their kind permission to publish these cases. We should also like to express our gratitude to Messrs. Smith, Kline and French of Philadelphia for the very generous supply of "Resodec" with which these patients were treated.

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THE AETIOLOGY OF CARCINOMA OF THE BODY OF THE UTERUS*

BY

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CARCINOMA of the body of the uterus is an interesting disease in that it is frequently associated with a number of natural phenomena which, I believe, may give some clue to its aetiology. These phenomena at first sight appear diverse, but on further examination appear to be linked together quite closely.

A review of the literature on this disease shows that many workers the world over have realized that carcinoma of the body of the uterus is frequently found in association with other pelvic lesions and with some lesions which are not pelvic and which do not properly come under the aegis of the gynaecologist. The menopause is said to occur later in women with carcinoma of the body of the uterus than in normal women; diabetes is common; uterine polypi and endometrial hyperplasia are frequently seen *in uteri* containing carcinoma; a high incidence of feminizing ovarian tumours has been reported; fibroids are alleged to be common concomitants of endometrial cancer; patients are alleged to be obese and there is more than one suggestion in the literature that there is an inherited predisposition to the disease.

It is my purpose in these lectures to show firstly that these statements are true and secondly to show the likelihood of a single factor being responsible for all these diverse conditions as well as for uterine carcinoma.

MENOPAUSAL AGE

It is essential at this stage to understand what is really meant in everyday gynaecological practice by the age of the menopause. It is simply the age at which the patient ceased to menstruate. The menopause is obviously a complex phenomenon of which cessation of the menses is only a small and probably not very important part. There seems little doubt that some ovaries function after the menopause because one not infrequently encounters women who, many years after the cessation of the menses, are subjected to oöphorectomy and who experience for the second time severe menopausal symptoms. Histological studies of such ovaries usually give no clue whatsoever to their function.

At what age can one normally expect a woman to stop menstruating? It seems essential to know this before we can discuss whether or not the menopause is late. The published figures in the literature seem to favour some time between the 46th and 48th years. The Medical Women's Federation investigation into this matter in 1933 showed that of 966 women examined 71 per cent ceased to menstruate before 50 and 29 per cent continued after that age. In an analysis of 536 patients admitted to the Gynaecological Department of the Royal Victoria Infirmary in the year 1938 who were over 50 years of age I found that 65 per cent had ceased to menstruate before 50; 31 per cent had ceased to menstruate after 50 and that 4 per cent were still menstruating at 50 or over (Table I). The average age of the menopause in my series was 46·5 years but in actual fact 61 per cent of these patients stopped menstruating later than 46·5 years, the average being reduced by the relatively large number of women in this group who had ceased to menstruate before 30. A better method is to establish the numbers who

* Ingleby Lectures for 1953 delivered at the University of Birmingham.

TABLE I

Menopausal age

(Gynaecological Department, Royal Victoria Infirmary, Newcastle upon Tyne, 1938)

Total	Menopause before 50	Menopause after 50	Still menstruating at 50
536	338 (65)	168 (31)	30 (4)
	(Medical Women's Federation Investigation, 1933)		
966	679 (71)	287 (29)	—

Percentages in brackets.

ceased to menstruate at any given year of age. If this is done it is found that the largest single group (11 per cent) ceased to menstruate at the age of 50. Nevertheless in all analyses that have been published the majority of women do appear to stop menstruating before 50 and menstruation after the age of 50 is the exception rather than the rule.

Crossen and Hobbs (1935) were the first to draw attention to the fact that women with carcinoma of the fundus of the uterus ceased menstruating later than normal women. Table II shows their figures and those of my own series side by side and it will be seen from this table that in both series more than half the cases of

TABLE II

Menopausal Age

Age Group	Fundal Cancer		Controls	
	Crossen and Hobbs	Way	Crossen and Hobbs	Way
	Per cent	Per cent	Per cent	Per cent
36-39	2	7	12	5
40-44	4	8	26	26
45-49	30	19	41	52
50-55	60	54	15	15

fundal cancer had ceased to menstruate later than 50 as opposed to only 15 per cent of patients who had ceased to menstruate after 50 but who did not have fundal cancer.

Chart 1 shows a graph of the age at which menstruation ceased in my control group of 506 patients without cancer compared with a group of 153 cases of carcinoma of the uterine fundus. The results are striking. From the age of 41 to 49 there are significantly less women ceasing to menstruate in the cancer group than in the normal group. At 49 years the graphs cross and from then on there are more ceasing to menstruate in the cancer group than in the control group, and these figures reach statistical significance at every point except the age of 51 years. The largest number of patients with carcinoma of the

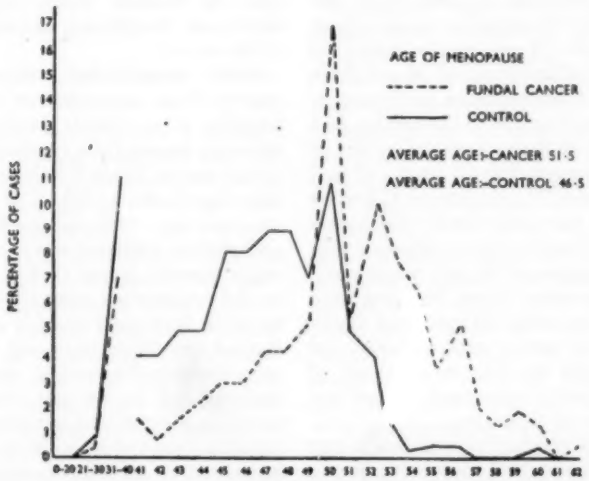

CHART 1

fundus ceasing to menstruate in any one year of age is at 50 (17 per cent) and this peak is also reached in the control cases (11 per cent) but the differences are statistically significant. The average age of the menopause in the cancer group is 51·5 years or 5 years later than those in the control group.

It has been said that these findings are due to a confusion of the bleeding due to the growth, with menstruation. A further examination of my cases shows that this is not so. It is possible that in the case of a patient with carcinoma of the body of the uterus who is admitted with the disease and claims to be still menstruating after the age of 50 that confusion can exist. I found 13 such cases. If, for the sake of argument, one assumes that they stopped menstruating at or before 50 and that the bleeding was due to cancer then in 6 of my 13 cases the cancer must have been present for 6 to 12 years, since their ages ranged from 56-62, and this hardly seems credible. In 7 cases, aged between 51 and 55, it must have been present from 1 to 5 years and here I will concede the possibility. In 69 cases menstruation had ceased after the age of 50; there had then been a period of amenorrhoea and this had been followed by bleeding due to the growth. I cannot think that where a clear-cut history such as this is obtained there could be any grounds for confusion. In only 19 (27 per cent) of my cases was this period of amenorrhoea less than 6 years. In 73 per cent of cases the periods had ceased after the age of 50 and there had been a period of amenorrhoea for 6 years or longer and then bleeding due to the tumour had commenced. In 26 of these cases the period of amenorrhoea was longer than 10 years and in 3 cases it was 22, 26 and 28 respectively. If anyone seriously suggests that endometrial carcinoma can arise and bleed and cause an apparent prolongation of the menstrual life of a woman and then without treatment stop bleeding and remain quiescent for nearly 30 years and finally start to bleed again such a person should not only have found out by now the aetiology of carcinoma of the fundus but an entirely new and more rational form of treatment.

It seems to be established beyond doubt that women with this disease tend to menstruate to a later age than do other women.

Diabetes

There are, as I have said, frequent references in the literature to the fact that diabetes is a common concomitant of endometrial cancer. Indeed it was by noticing, some years ago, the frequent occurrence of diabetes in cases of carcinoma of the body, as compared with the rare occurrence of it in carcinoma of the cervix in my own clinic, that my interest was first aroused in these matters which form the subject of these lectures.

Before discussing this further it is necessary to realize that there are two forms of diabetes mellitus. The first is the so-called pancreatic type or insulin sensitive diabetes which is seen more frequently in young people, which tends to be very severe, with frequent comas if not treated, and which shows a marked response to insulin. Even in these days it is still a very serious disease. The second type is the insulin resistant or senile type often called "pituitary diabetes". This occurs almost entirely in much older people than the former type and is much commoner than pancreatic diabetes. It is often mild and responds well to dietary measures. Coma is rare and the response to insulin very poor. Unlike pancreatic diabetes, which attacks both sexes, the senile type of diabetes is very much more common in women than in men, and it is this type of diabetes which, in my experience, exclusively complicates carcinoma of the body of the uterus.

From America come estimates of the frequency of the association of these two diseases. Scheffey *et al.* (1943) found 11 per cent of diabetics among their carcinomas of the fundus of the uterus. Moss (1947) using glucose tolerance tests found 11 out of 23 cases. Palmer and his associates (1949), using a fasting blood sugar and glucose tolerance where the fasting reading was abnormal, found 16·9 per cent of diabetics in 165 consecutive cases of carcinoma. In our series in Newcastle glucose tolerance was performed on 106 patients and 31 or 29 per cent were diabetic. Twelve had clinical symptoms of diabetes and 19 had not, although 4 of these have since developed symptoms. Five of these patients were known to be diabetic before their admission on account of cancer, all having been diagnosed clinically. Eleven were discovered on

admission for treatment of the cancer, 2 clinically and 9 by glucose tolerance and 15 were diagnosed after the cancer had been treated, 10 by glucose tolerance and 5 clinically.

Many other cases as we shall see later showed a prediabetic type of curve with a raised fasting blood sugar, a high rise, and a curve which at the end of 2 hours was still more than 40 per cent above the fasting level. Some of these curves were still climbing at 2 hours but, unless the 2 hour level was above 300 mg. per cent and there was sugar in the urine, I have not classified them as true diabetics although in some cases I might have done so with justification. Almost everyone of these patients showed a raised threshold for sugar and one did not develop glycosuria until the blood sugar reached 475 mg. per cent. Only 28 per cent of our cases of carcinoma of the body of the uterus had a normal sugar curve. Our estimate of 29 per cent is probably a conservative one. We do not know the incidence of diabetes among the population of this country and the only person who has offered such an estimate in the literature is Palmer of Buffalo who quotes the work of Spiegelman and Marks (1946). In 1,300,399 females over the age of 35 they found an incidence of 1·02 per cent. On this estimate clinical and sub-clinical diabetes would be 28·4 times as common in my uterine cancer cases as in the general population.

Uterine Polyps and Endometrial Hyperplasia

Benign endometrial hyperplasia is a common enough finding in women, especially near the menopause. After the menopause it is rare. Speert (1949a), in a study of 60 normal uteri removed after the menopause, found only 3 cases of adenomatous hyperplasia and 2 of these had received synthetic oestrogens. He did, however, find 17 endometrial polyps. Novak and Yui (1936) reported 25 cases of endometrial hyperplasia co-existing with carcinoma of the endometrium, and they expressed the belief that post-menopausal hyperplasia is a premalignant lesion. Hertig and Sommers (1949), studying the previous histories of a series of cases of carcinoma of the fundus of the uterus, found that adenomatous hyperplasia of the endometrium was relatively most common in a period of 1 to 5 years preceding the development of the carcinoma and that it was both most often observed and found to show a definite trend to increasing incidence as cancer developed. My own cases show nothing to contradict these statements and we have frequently found carcinoma in one part of the uterus and benign hyperplasia in others.

Scheffey found 7·8 per cent of his cases co-existing with polyps of the endometrium and Barns (1942) 5·3 and Hertig and Sommers (1949) 12 per cent. We have been very much interested in endometrial polyps, but in 66 of our cases, either because they are old cases treated before this work was commenced, in which we were unfortunately not so particular in our recording, or because they were treated radiotherapeutically, we have no record about polyps. In 90 cases our information is complete. In 24 cases, benign polypi co-existed with a carcinoma and in 6 others the tumour itself was a malignant polyp, an incidence of 33 per cent.

I have grouped these two conditions together because I believe that they are really the same thing and that polypi are nothing more than localized areas of benign hyperplasia.

Feminizing Ovarian Tumours

Functional tumours of the ovary always arouse great interest and are very well documented in the literature. The occurrence of cancer of the endometrium in association with these tumours seems, from the literature, to bring about the immediate acceptance of the fact that cancer of the endometrium is produced by oestrogens, but it is not quite as simple as this, as I hope to show later.

Diddle (1952) reviewed the literature on these tumours very exhaustively and among 1,189 published reports of granulosa cell tumours and thecomas of the ovary he found recorded 73 endometrial cancers as opposed to 5 cervical tumours. He found that cancer was 4 times more common with thecomas than with granulosa cell tumours and that in 1 in 10 women with associated uterine disease, this associated disease was endometrial carcinoma. Ingram and Novak (1951) and also Dockerty and Mussey (1951)

drew attention to the fact that carcinoma of the endometrium only existed with these tumours in older women, that is women past the age of 50.

In our series there were 5 feminizing tumours in 89 cases. Both carcinoma of the body of the uterus and feminizing ovarian tumours can hardly be called common diseases and this frequent co-existence appears to be more than coincidental.

Obesity

The general idea of the woman with endometrial carcinoma appears to be an enormous individual, with a face rather like the popular idea of a publican's, who provides the surgeon with a very tough assignment. This, of course, is just another medical impression and the thin easy hysterectomies for cancer of the uterus are forgotten like the normal delivery conducted at lunch time by the midwife. It is the Caesarean section at 2 a.m. that is responsible for that other erroneous statement that all babies are born at night.

Weight is not the only factor. Height and weight must be considered together. A woman 4 ft. in height weighing 10 stones is terribly obese but a woman of 6 ft. 4 in. weighing 13 stones is positively skinny. We have tried to allow for this is our estimations of obesity and in 88 patients on whom we have information on this subject 44 were obese and 44 were not. However, in a series of normal women only 27 per cent were obese and the difference 23 ± 8 is statistically significant.

Fibroids

The incidence of fibroids among the general population is quite unknown, and the frequent statements which appear in most text-books of gynaecology that 30 to 40 per cent of women suffer from fibroids is grossly erroneous. In gynaecological clinics the incidence of fibroids, which must of course be many more times greater than in the normal population, does not reach this figure. Most recent estimations of the co-existence of corporeal cancer and fibroids place the figure at about 30 per cent. In my series, out of 92 cases upon whom we have information, 31 had fibroids, an incidence of 34 per cent.

Bland-Sutton (1909) in his writings on fibroids stressed the frequency with which corporeal cancer was found and Noble (1906) found corpus cancer 8 times more frequently than cervical cancer in his series of 2,274 operations for fibroids. I seldom see fibroids in cases of carcinoma of the cervix yet, as I have said, more than a third of my corpus cases have these tumours in addition to their cancer.

Inherited Predisposition

Suggestions that heredity plays a part in the development of cancer of the body of the uterus have been made from time to time and some of these suggestions were made a very long time ago. Most of the records, however, are confused by the pernicious habit that doctors in general have of talking very loosely about uterine cancer. I would like, for a moment, to digress on this subject as I consider it to be of some importance.

Our genetic studies are a recent adventure but almost as soon as they started we came up against every difficulty that had confronted every other investigator in the field. Firstly, there is the fundamental difficulty that the experimental animal lives as long as the investigator and therefore he who starts the experiment will not finish it. This is discouraging because it needs a more than ordinary unselfish outlook to start something which someone else will get the credit for. Having started the work there are innumerable difficulties in the way. Firstly the information has to be extracted from some member of the family as to the fate and whereabouts of her relatives and this has to be checked. Wilfully false information is hardly ever a difficulty but the fact that various members of the family have ceased to have anything to do with the other members has been a very great difficulty and calls for much tact to overcome, indeed if it can be overcome at all. There is frequently need to trace relatives who are dead and this is a source of great trouble. Hospital records are often very scanty indeed and the co-operation which we have received from general practitioners has been negligible in most cases. There remains, in the case of a deceased person, the office of the Registrar General, but we have found that the certificate of death from the

scientific point of view is completely inaccurate. Of 35 recent deaths from carcinoma of the body of the uterus which were registered at the Newcastle Regional Cancer Bureau only 8 were correctly certified and 4 of these had been certified in my own unit. Seven were certified as carcinoma of the cervix and 20 as unspecified uterine cancer. Everyone who has worked on the genetics of this disease has come up against the problem of this unspecified uterine cancer. Now carcinoma of the body of the uterus differs from carcinoma of the cervix just about as much as leprosy differs from smallpox. Not only are there histological differences but the mode of spread is different, the response to treatment is different and whatever the aetiology of cervical cancer it is certainly not the same as that of corporeal cancer. Even great authorities are not exempt from this slack terminology "uterine cancer". Ewing (1940) in the last edition of his book *Neoplastic Diseases* writes a chapter on both forms of uterine tumour and the result is really confusing. I would plead for a much more careful differentiation of cervical and corporeal cancer in all levels of medicine and at the same time I would warn you that the growing number of papers based on the statistical analysis of the causes of death as certified on death certificates are not worth the paper they are written on. Nothing can take the place of careful extensive documentation which means hard work with pencil and paper. Only after you have done that can you get out the slide rule and the log tables so beloved by the mathematician but you cannot get out of statistics more than you put in.

The early records of the genetics of cancer of the uterine fundus are meagre and mostly concern mothers and daughters or several sisters all of whom died of the same disease. Halliday Croom in 1912 published a record of twin sisters who commenced to menstruate on the same day, both developed menorrhagia at the age of 30, both ceased to menstruate at the age of 50 and both, at the age of 53, were admitted to hospital, one in Glasgow and one in Edinburgh with endometrial cancer and degenerating fibroids.

Purdie (1945) recorded endometrial cancer in sisters aged 32 and 34. We have found some families among our patients with several examples of the disease. Fig. 1 shows a very anaplastic endometrial carcinoma in one of my patients. This patient's mother had died of "uterine cancer", and the mother's sister, an old lady of 85, had been a diabetic for many years. When she was visited in order to complete the family history it was found that she had had a recent vaginal haemorrhage and 2 months later at her death from diabetes we performed an autopsy and removed the corporeal cancer shown in Fig. 2. It is of interest to note the apparent high degree of malignancy in both these tumours for this degree of malignancy is not frequently seen in carcinoma of the body of the uterus.

Brobeck (1949) undertook a statistical survey of the familial influence on this disease. He found more tumours among the sisters and mothers of his patients with carcinoma of the body of the uterus than he did among his controls but he qualified these statements because he, like us, came up against this old problem of unspecified uterine cancer in his control cases. He found several cases with more than one example of carcinoma of the body in the family and he concluded that these conditions pointed to a hereditary predisposition.

Finally, on the subject of genetics I would draw attention to the famous family G. of Warthin. G. was a German who emigrated to America and settled in the State of Michigan in the region of Ann Arbor. He knew that his family had a reputation of dying of abdominal cancer. His wife had no such family history. G. died in 1856 of abdominal cancer. He left 10 children, 5 girls, 2 of whom died of endometrial cancer and 1 of whom died at 26 before she could develop cancer, and 6 boys, 5 of whom died of cancer of the stomach or large bowel. He had 62 grandchildren, 8 of whom died before reaching the cancer age. Of the 54 remaining 27 died of cancer, 11 of them of endometrial cancer. Of 104 great-grandchildren attaining the age of 25, 7 had developed cancer, including 2 endometrial tumours up to 1936 when this family was last reported in the literature. At that time there were 89 offspring of further generations not yet 25 years old. Only 1 of G.'s sons escaped cancer and he died at 84 leaving no children. Two daughters escaped and none of their children or grandchildren developed cancer. A third daugh-

ter, who died very young and about whom the cancer potentialities are unknown, had a son who died of gastric cancer and his 3 children were lost trace of and no further information about that branch of the family is forthcoming. This latter woman was a twin sister of one of the daughters who with her offspring escaped the family taint but it is not known whether they were identical twins. No cases of cancer of the cervix occurred in this family.

We may summarize by saying that in carcinoma of the body of the uterus the menopause occurs later than in women without cancer; that the senile type of diabetes is common; that uterine polypi and endometrial hyperplasia as well as feminizing ovarian tumours and fibroids frequently co-exist and that obesity appears to be not uncommon. In addition there are strong indications that carcinoma of the body of the uterus may show a familial tendency.

Let us now examine these phenomena from a slightly different angle.

Late Menopause

We decided early in this work that we must make a special study of women whose menopause occurred after 50 and who at the time we saw them had not developed endometrial cancer. There were 133 such women who came under our care with a very wide range of diseases varying from prolapse to carcinoma of the cervix. All these patients had glucose tolerance tests performed and none of them at the time was known to be diabetic. Chart 2 shows, however, that 12 per cent were true diabetics and a further 41 per cent were pre-diabetic. On the chart are three groups of cases: fundal carcinoma; patients with a late menopause and patients who were not suffering from carcinoma of the uterus and who had experienced a cessation of their menses before the age of 50. In this latter control group only 3 per cent were diabetic and no less than 67·4 per cent had a normal glucose tolerance.

The differences in the diabetics in these three groups are statistically significant but the differences in the pre-diabetics are not, except between the fundal carcinoma group and the control group (Table III). If the curves are added together into normal and abnormal the differences between each group are statistically significant. Five of the pre-diabetics in the late menopause group have now developed diabetes but are not so recorded in this paper.

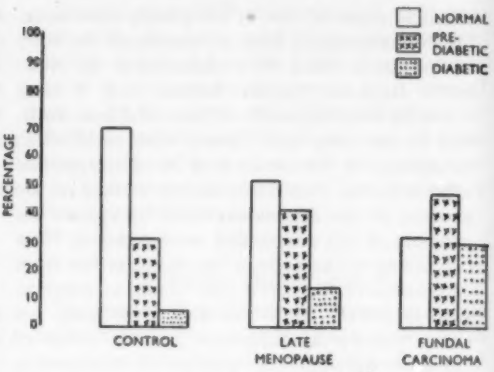

CHART 2

TABLE III

Glucose Tolerance Curves
(Carcinoma, late menopause and control)

	Normal	Abnormal
Carcinoma ..	30 (28)	76 (72)
Late menopause ..	62 (47)	59 (53)
Control	39 (67)	19 (33)

Percentages in brackets.

Two criticisms may be levelled at this. They are that the conclusions that can be drawn from this table may be invalidated because it is said that advancing age and obesity will both cause an increase in the number of abnormal glucose tolerance tests. We were careful at the outset to pick our controls from the same age groups as the fundal cancers and the late menopauses and these were picked practically case for case; thus of all the patients from each group there are equal percentages in each age group.

Many papers have been written to show the influence of age on the glucose tolerance and all workers seem to assume that the passing of the years is responsible for the alterations noted. This is not so. The passing of the years *per se* is responsible for nothing.

You will have read recently that the fabric of

Westminster Abbey has suffered damage with the passing of the years. Now the damage has been due to the collection of soot, dirt and noxious gasses. The years have only influenced the matter in so far as the longer the building has stood the more noxious influences have worked on the fabric. If Westminster Abbey had been kept always in a vacuum it would now be as good as new. If in the first year of its life it had been exposed at once to the sum total of sulphur dioxide which has accrued in 1,000 years none of us would ever have seen it. So with the glucose tolerance. It is not the passing of the years but something that happens during that time and in women that something is without doubt the profound endocrine changes which accompany and follow the menopause.

Obesity has been shown to be accompanied by disturbances of carbohydrate metabolism which can block the action of insulin. Table IV shows

TABLE IV

Glucose Tolerance in Obese and Normal Cases

	Percentage figures					
	Obese			Normal		
	Diabetic	Pre-diabetic	Normal	Diabetic	Pre-diabetic	Normal
Carcinoma	32	48	20	34	34	32
Late menopause	12	48	39	9	37	54
Control	0	23	77	6	26	68

There are no statistically significant differences between the obese and the normal in either carcinoma or late menopause or the control group.

the differences in the glucose tolerance test in each of the groups according to whether the patients were obese or not. You will see that although in a downwards direction there are significant differences there are no significant differences transversely on the table, that is to say that the differences in the number of diabetics, pre-diabetics and normal curves depend on factors concerning the presence or absence of carcinoma or a late cessation of the menses and not on whether the patient is fat or thin.

Diabetes

The next task which we set ourselves was a study of diabetics from a diabetic clinic. I was able to interview 88 female diabetics of all ages who were attending the clinic.

The age at diagnosis. The age at diagnosis in these women was almost the same as the age at diagnosis in our cases of carcinoma of the body of the uterus and Chart 3 shows that the peak age of the diabetics is about 5 years later than that of carcinoma of the corpus, which accords with our finding that most of the diabetics in our series of cancer of the body of the uterus were diagnosed after treatment of their cancer. Thus it seems that not only is diabetes frequently associated with carcinoma of the uterus but that the two diseases occur at approximately the same time in the life of the woman.

Date of the menopause. The next feature from the diabetic study was the date at which the menopause occurred. Of 70 of these 88 patients who had ceased to menstruate, 37 or 54 per cent had ceased to menstruate after the age of 50, a much higher incidence than we have found in our normal controls, referred to above, and only slightly lower than those of our cancer cases. Thus in two respects, namely age at diagnosis and age at the cessation of the periods, diabetes and cancer of the endometrium, even when not associated, appear to show the same tendency.

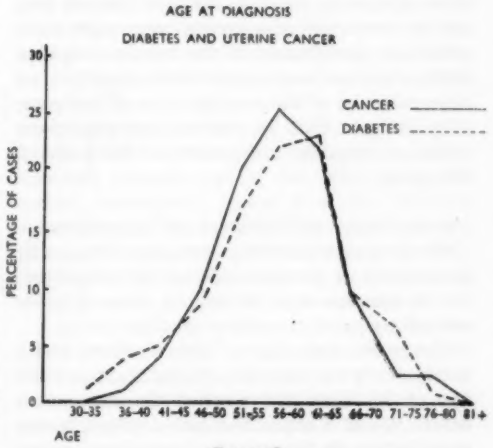

CHART 3

Much experimental work has been carried out since 1930 on the aetiology of diabetes by Houssay (1942) and his co-workers in the Argentine and by F. G. Young (1951) in Cambridge. For a large number of years, mainly due to the work of Cushing, glycosuria was thought to be due to lesions of the posterior pituitary. In 1930 Houssay and Biasotti showed that total hypophysectomy ameliorated pancreatic diabetes but that subsequent injection of anterior pituitary extract intensified it.

F. G. Young in Cambridge using a crude saline extract of anterior pituitary produced severe diabetes in dogs, and has subsequently produced it with purified extracts of anterior pituitary growth hormone. He explains, in the case of purified extracts, however, that he is uncertain whether the effect is not produced by slight contamination with other pituitary hormones. These diabetogenic growth-producing extracts when given to puppies and kittens produce growth and not diabetes, but in the adult animal where body growth is already completed injection of these extracts resulted first in an initial rise in body weight and then in the development of diabetes. A characteristic of Young's animals was the development of a large roll of abdominal fat which would appear to correspond to similar rolls not infrequently seen in women with carcinoma of the uterine fundus. Young failed completely to induce diabetes with these extracts in pregnant animals. Instead they deliver themselves of a greatly overweight litter somewhat reminiscent of the human pregnant diabetic and her large babies. Here, therefore, we have evidence of the anterior lobe of the pituitary being at fault in one of these conditions which accompanies carcinoma of the body of the uterus.

Uterine Polyps and Endometrial Hyperplasia

We have seen that these conditions frequently accompany or precede endometrial carcinoma. Let us examine more closely 32 cases of endometrial polyps that we have studied.

Firstly the menopause. Table V shows that 3 patients only were pre-menopausal and below the age of 50. Five had reached the menopause before 50 and 5 others had had a radium menopause before 50. Fourteen had ceased menstruating after 50 and 5 were still menstruating regularly after 50; thus of 24 who were past 50 and had not had a menopause induced artificially 79 per cent continued to menstruate beyond the age of 50.

TABLE V

Endometrial Polypi. Age of the Menopause

Total	32
Menopause not reached (under 50)	3
Menopause before 50	5
Radium menopause before 50 ..	5
Menopause after 50	14 (43·7 per cent)
Still menstruating after 50 ..	5 (15·6 per cent)

Fig. 3 shows an endometrial polypus. The patient from whom this polypus was removed was operated on in 1938 for prolapse. She had ceased to menstruate in 1934 when she was 53 years of age. In 1949 she developed diabetes and in 1951 when she was 70 she came under my care with recurrent prolapse for which I performed a vaginal hysterectomy. This polyp was found in the removed uterus and was symptomless.

I have asked my medical colleagues to let me remove the uterus post mortem on all diabetics who have died in hospital. So far only 4 cases have come my way. None had apparently had any gynaecological symptoms yet each uterus contained a polyp and Fig. 4 shows one of these.

Speert (1949b) as a result of a case of acromegaly and granulosa cell tumour found an endometrial polyp in the uterus and reviewed the literature. He found this to be scanty on the subject of the uterus in acromegaly. This disease, of course, as is well known, is due to over-action of the anterior pituitary. Three cases in addition to Speert's were found to have endometrial polypi and acromegaly. Since Cushing himself was only able to find 4 cases of acromegaly in which the uterus was adequately described this would appear to be a high incidence.

We have removed the uterus in 12 patients who were known to have had endometrial hyperplasia and whose menopause had occurred after the age of 50. All 12 were symptomless as far as uterine cancer was concerned. Some had fibroids, some had prolapse in which vaginal hysterectomy was performed and in the 12 removed uteri 3 totally unsuspected carcinomas of the body were found. Fig. 5 shows one of

them. Everyone of these patients fitted into our concept of the type of patient mentioned in this lecture, namely that they had one or more or all of the following: family histories of corpus cancer, obesity, polypi, late menopause and abnormal sugar curves. The remaining 9 showed hyperplastic endometriums, although they were all past the menopause (Fig. 6). It must be realized that this particular part of the work is largely experimental and I do not advocate the wholesale removal of uteri in such cases; indeed, we are now watching closely a series of this type of case in order to see what happens to them. I do, however, feel that the uterus which contains a polyp after the menopause, especially where this has occurred after the age of 50, and if the patient is a diabetic, is a menace and should be removed.

Feminizing Tumours

In this clinic I have only been able to find 8 cases so that I am in a large degree dependent on the observations of others for my remarks on this subject. Table VI shows the age of the cessation of the menses in 41 cases, including my own, in which I have been able to get information on this subject. The 41 cases consist of 23 thecomas and 18 granulosa cell tumours. Of these patients slightly more than half continued to menstruate until after the age of 50. If they are divided according to histology many more thecomas are associated with a late menopause than granulosa cell tumours. We have seen previously that corporeal cancer is commoner with thecoma than with granulosa cell tumours and it is at present considered that the oestrogen secretion of granulosa cell tumours is dependent on the presence in these tumours of thecomatous elements. The literature is strangely silent except for odd references on the question of diabetes. In my series of 8 cases there was 1 diabetic, 6 prediabetics and 1 patient had a normal glucose tolerance.

TABLE VI

Feminizing Ovarian Tumours
Age of Menopause
(Personal cases and from literature)

All types of tumour		
Total	41	
Menopause before 50	20	(49 per cent)
Menopause after 50	19	
Still menstruating at 50	2	
Granulosa cell tumours		
Total	18	
Menopause before 50	10	(55 per cent)
Menopause after 50	7	
Still menstruating at 50	1	
Thecomas		
Total	23	
Menopause before 50	10	(44 per cent)
Menopause after 50	12	
Still menstruating at 50	1	

Since the last war some intensely interesting experimental work on the production of feminizing tumours has been carried out particularly by Biskind and Biskind (1949) and Li and Gardner (1947). This work has shown most conclusively that if an animal is castrated and one of the ovaries is transplanted into the spleen the graft will grow. Now provided no adhesions to the abdominal wall take place all the secreted oestrogen must pass through the liver since it can only get into the portal system. Oestrogens are destroyed in the liver and cannot therefore reach the pituitary. The result of this state of affairs is that at first a collection of lutein cells appears and later as the graft grows granulosa cell tumours arise. If the animal's pituitary is removed the graft either fails to take or if it has already taken it perishes unless the animal is injected with anterior pituitary extract. Clearly then the pituitary finding itself removed from the restraining influence of oestrogen can act unopposed on the ovarian tissue of the graft and by its action produces these tumours. It takes some time for this tumour formation to take place. No luteomas formed before the 150th day after the splenic graft had been performed and no granulosa cell tumours before the 300th day. The earliest oestrogenic smear that the Biskinds observed was 346 days, and they believed that this was due to the graft secreting so much oestrogen that the liver could not cope with it all and that some got into the systemic circulation.

Endometrial polyps are common in association with feminizing tumours. Falls, Ragins and Goldenberg (1949) found them present in 13 per cent of cases whilst Diddle (1952) in his review of the subject found that endometrial polyps occurred "twice as frequently as cervical ones". Novak

and also Mussey observed that carcinoma was only seen in association with feminizing tumours in women after the age of 50. They suggested that this was due to the fact that a long continued secretion of oestrogen was necessary to bring about the development of carcinoma. Woll *et al.* (1948) have suggested that the development of feminizing tumours may be due to the presence of endometrial carcinoma, but I would like to put forward the suggestion that both are the result of a common pituitary stimulus.

Obesity. I have referred already to obesity. It remains for me to emphasize that among the diabetics that I have studied 57 per cent were obese and that in my control cases there were significantly less obese patients than in the cancer cases or the late menopause group or the diabetics (Table VII).

TABLE VII

Distribution of Obese and Normal Patients

	Obese	Normal
Carcinoma ..	44 (50)	44 (50)
Late menopause ..	56 (49)	57 (51)
Control	13 (27)	34 (73)

There are significantly less obese patients in the control group than in either of the others. Percentages in brackets.

Fibroids. We have not yet had time to study a series of cases of fibroids and it is one of the many incomplete parts of our work. However, 34 per cent of our cancer cases had fibroids and among the 88 diabetics 6 (7 per cent) had had operations for fibroids, and 4 had had endometrial polyps removed. The incidence of fibroids with feminizing tumours is very high. In Falls' series it was 45 per cent which is exactly the same figure as Novak found in a series of 135 cases of feminizing tumours. Diddle, in a review of the world's literature on feminizing tumours found 40 per cent of fibroids which he found were more common with thecomas.

Before proceeding to the final part of this lecture I would like to consider for a moment the conditions which necessitated the admission to hospital of the cases in which I estimated the age of the menopause shown in a previous table.

Five-hundred-and-six of the 536 women had ceased to menstruate; 187 of them were admitted for malignant lesions and 349 for benign lesions. Table VIII shows the malignant group in

TABLE VIII

Age at the Menopause of Patients admitted to the Gynaecological Department with Malignant Lesions

Lesion	Total	Menopause before 50	Menopause after 50	Percentage after 50
Carcinoma of Cervix ..	128	93	35	27
Carcinoma of body of uterus ..	20	8*	12	60
Carcinoma of vulva	16	11	5	31
Carcinoma of ovary	10	6	4	40
Miscellaneous malignant conditions	13	9*	4	30
	187	127	60	32

* Includes one diabetic.

which 32 per cent had a late menopause. The incidence of late menopause was highest in carcinoma of the corpus (60 per cent) and lowest in carcinoma of the cervix (27 per cent). Table IX

TABLE IX

Age at the Menopause of Patients with Benign Lesions

Lesion	Total	Menopause before 50	Menopause after 50	Percentage after 50
Prolapse	136	94	42	31
Benign ovarian tumours ..	29	21	8	27
Post-menopausal bleeding (non-malignant)	23	19	4	17
Fibroids	21	8	13	62
Cervical erosion ..	14	10	4	28
Cervical polyp ..	14	7	7	50
Endometrial polyp	11	5	6	55
Urethral caruncle	11	8	3	27
Benign lesions with diabetes ..	6	2	4	—
Granulosa cell tumours ..	3	0	3	—
Miscellaneous benign conditions	51	37	14	27
	319	211	108	33

Thirty other patients were admitted still menstruating regularly at 50 or over. All were suffering from benign endometrial hyperplasia.

shows that in women admitted for benign lesions the group as a whole showed 33 per cent continuing to menstruate after 50. This figure of 33 per cent was considerably exceeded in polyps, both endometrial and cervical and in fibroids. Although the figures are small it is of interest to note that in 6 diabetics with benign lesions, 4 had a late menopause and in 3 feminizing tumours all of them menstruated beyond the age of 50.

I have tried to find out what has subsequently happened to these women with a late menopause but the war years have intervened and I have been particularly unsuccessful. Of those we have been able to trace, diabetes, fibroids and ovarian thecomas appear to be the commonest subsequent diseases. As far as we can detect none of them died with endometrial cancer. However, we were unable to trace nearly three-quarters of them some 15 years after they were admitted.

Heredity. Our studies on this subject, as I have said, have been full of frustration. Nevertheless of 12 families of patients with carcinoma of the fundus, 85 male and female relatives have been traced and we have found 8 diabetics and 7 cases of cancer of the corpus. With regard to the age of the menopause we have no family in which the patient ceased menstruating after 50 where either her mother or a sister did not also have the menopause later than one would normally expect. I was able to determine the menopausal age in 35 relatives of the diabetics and it occurred before 50 in 9 and after 50 in 26.

In 41 per cent of diabetic cases there was a known family history of the disease. I found 6 female relatives with fibroids and 3 with carcinoma of the corpus. Pincus and White (1934) have shown that the diabetes is inherited as a recessive and Brobeck (1949) has some evidence to support a similar claim for cancer of the corpus. Our work suggests that the menopausal age is predetermined genetically and Warthin (1925) thought that his family showed a recessive inherited predisposition to cancer.

Wells, in 1923, using both animal and human material concluded that the human material was insufficient to draw conclusions but that from animal experiments, particularly those of Maud Slye, the susceptibility to cancer is inherited as a Mendelian recessive; the power to resist it is inherited as a Mendelian dominant and that the site and character of the tumour are also inherited. Inbreeding is not in itself responsible for cancer but of course the results of inbreeding from a susceptible strain are only too obvious. Greene and Newton (1948) have more light to throw on this problem in the case of the rabbit. The rabbit is the one experimental animal which develops endometrial cancer with any frequency. They have shown that 17 per cent of female rabbits, over the age of 2 years, suffer from this disease and with increasing age the percentage becomes higher.

If endometrial cancer is transplanted from one animal to a normal animal the focus will remain but will not grow. If, however, it is transplanted into an animal that already has cancer of the uterus or into one of its relatives, the cancer will grow. Only a few well established cancers will "take" in normal animals. Thus it seems that the factors necessary for the development of endometrial cancer must be present to support the growth of the transplant.

It may well be supposed that, if genetics plays a part in the development of endometrial cancer, its influence may vary from district to district or country to country or race to race. There is some evidence that this does actually happen. Although the true incidence of cancer of the corpus cannot be determined one can compare it with other forms of malignant disease. In the Newcastle region we admit 7 carcinomas of the cervix to 1 carcinoma of the body of the uterus every year. This is not so in all parts of the country. Mr. John Stallworthy tells me that in Oxford their admission rates are only 2 carcinomas of the cervix to 1 carcinoma of the body of the uterus; whilst Mr. Robin Watson very kindly gave me some figures for the incidence of the two diseases in Northampton where the ratio is 100 cases of carcinoma of the body to 75 cases of carcinoma of the cervix. In both towns there are radiotherapy centres and we have been able to exclude the possibility of patients with cancer of the cervix going to other centres to receive radiotherapeutic treatment. The large number of cases of cancer of the body of the uterus reported from Stockholm by Heymans has for long puzzled me and it would seem probable that there are relatively more carci-

nomas of the endometrium in Sweden than we see in Newcastle.

Carcinoma of the fundus of the uterus is relatively more common in Jewesses than carcinoma of the cervix and the Jewish race are particularly prone to diabetes and to obesity. Finally, I am informed that, whilst, carcinoma of the cervix is extremely common among Japanese women, carcinoma of the endometrium is practically never encountered.

It would seem that there is some evidence to show that over-activity of the anterior pituitary may lead to many different manifestations as would be expected from an organ with so many diverse features as the pituitary. Thus not all the manifestations of this over-activity may be seen in the same patient; one may develop fibroids, another diabetes or carcinoma of the uterus whilst others may develop all or a combination of these diseases. One cannot also escape thinking that this tendency to over-activity of the anterior pituitary may be the one factor which is inherited.

In conclusion I would like to thank Dr. Ruth Dearing, Dr. Helen Johnson and Mr. Heslop, Senior Laboratory Technician, Queen Elizabeth Hospital, Gateshead, who were closely associated with the clinical part of this investigation; Dr. Alfred Glucksmann and Dr. Cora Cherry of the Strangeways Research Laboratory, Cambridge, and Dr. Claud Taylor, Birmingham and Midland Hospital for Women, who gave me so much help from the pathological aspect; my colleagues in the Departments of Gynaecology and Radiotherapy who have allowed me to see so many of their cases and particularly Professor Harvey Evers for his encouragement in these studies; Dr. C. N. Armstrong and Dr. George Hindson for permission to study the diabetics at the Queen Elizabeth Hospital, Gateshead, and the Scientific Committee of the Newcastle Regional Hospital Board for the grant which enabled Dr. Johnson to investigate the family histories of these patients, and finally but not least, John Stallworthy and Robin Watson for their figures of the incidence of carcinoma of the body of the uterus.

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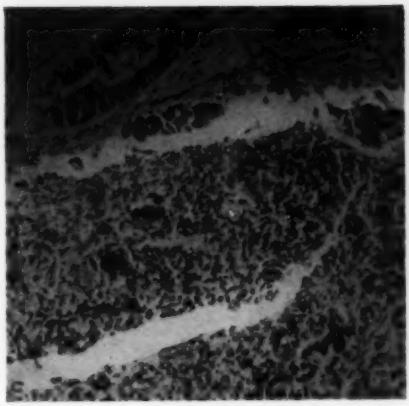

FIG. 1

Shows an anaplastic adenocarcinoma of the endometrium removed from patient M.S., aged 56, 1949. ×100.

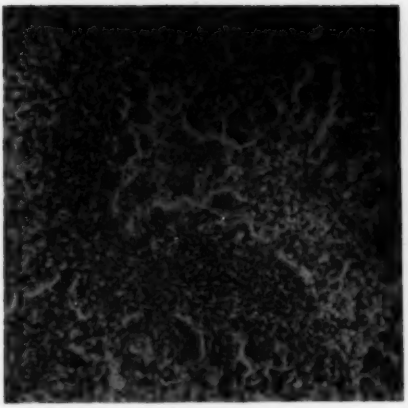

FIG. 2

Shows an anaplastic adenocarcinoma removed at autopsy from diabetic patient A.E., aged 85, 1951. ×100. (This patient was the sister of the mother of Mrs. M.S. whose tumour is shown in Fig. 1.)

FIG. 3

Shows a portion of uterine wall with attached endometrial polyp discovered accidentally at vaginal hysterectomy on a diabetic patient. ×3.

FIG. 4

Shows a portion of uterine wall with attached endometrial polyp removed at autopsy from a 63-year-old diabetic who died of peritonitis following cholecystectomy. ×3.

S.W.

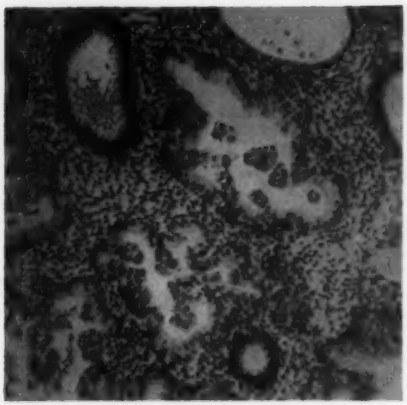

FIG. 5

Shows an unsuspected endometrial carcinoma and endometrial hyperplasia discovered histologically at hysterectomy in a woman aged 56 who had had a radium menopause at the age of 52 for benign hyperplasia. Curettage negative. ×100.

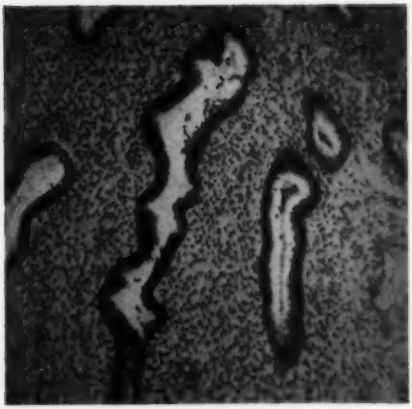

FIG. 6

Shows an active endometrium in a 70-year-old diabetic whose menopause had occurred at the age of 53. No symptoms. ×100.

S.W.

AN IMPROVED TECHNIQUE FOR THE INDUCTION OF LABOUR

BY

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THE readiness with which labour can be induced by medical or surgical means diminishes as the length of time before term increases, and this is especially so in the case of primigravidae. Pre-eclampsia frequently dictates induction of labour under these unfavourable circumstances, leaving Caesarean section as the only alternative.

If improved methods of inducing labour reduced the failure rate to insignificant figures, if the dangers of infection of mothers and foetus were practically eliminated, if rapid deterioration of "toxaemic" cases could be prevented and placental efficiency maintained, the indications for abdominal delivery especially of first babies would be materially reduced.

The "toxaemic" syndrome can be controlled by salt depletion, using an ion exchange resin to reinforce the effects of bed rest and a low salt diet on sodium metabolism (Carey, 1953), while the reduction in tissue oedema produced by the ion exchange resins may improve the efficiency of the placenta and reduce the risk of intra-uterine foetal death.

In 1,113 cases of induction of labour studied by Lemmon (1948) 942 were carried out in cases of toxaemia. Although rupture of the membranes was preceded by castor oil and enema and followed by intermittent hypodermic injections of pituitrin, 15 per cent were not delivered within 48 hours. After 48 hours the maternal morbidity rose from 9 to 17 per cent and the foetal mortality from 20 to 32 per cent. This emphasizes the need for more effective methods of inducing labour, combined with reduction of infection.

While intermittent intramuscular injections of pitocin are occasionally successful in precipitating the onset of labour, more often they are ineffective and sometimes they produce foetal distress.

In 1948 Theobald described a technique for the administration of pituitrin by continuous intravenous infusion. More recently it has been the custom to use pitocin instead of pituitrin as it is equally effective and avoids certain of the objectionable side effects of pituitrin.

Intravenous pitocin drips are not without their own dangers. Lund (1952) and Kaufman *et al.* (1953) have found that 3 per cent of women are excessively sensitive to pitocin and will develop tetanic uterine contractions with amounts of pitocin which are almost without effect in the average case. In excessive dosage pitocin or pituitrin, irrespective of the method of administration, will increase uterine tone and impair placental circulation. This hazard is accentuated in pre-eclampsia and hypertension, as Browne and Veall (1953) have shown that these conditions are associated with reduced placental reserve. If intravenous pitocin is given to multiparae without adequate care and supervision, the lower segment is liable to rupture, and 2 such cases have been reported by Ferguson *et al.* (1952).

When pitocin is given by continuous intravenous infusion the above dangers can be avoided by correctly assessing the optimum dosage rate. This rate varies due to the wide range of sensitivity to pitocin exhibited by different women, and by the fact that varying degrees of tolerance to the drug are developed after a few hours of continuous administration. These difficulties have been resolved, however, by using the method described below.

Pitocin given by intravenous infusion was used to induce labour in 7 toxaemic cases by Mauzy and Donnelly (1952) and in 100 cases, of which 6 were toxaemic, by Kaufman *et al.* (1953) without any change in the blood-pressure. Likewise, Friedman (1953) successfully induced 4

cases of eclampsia without significant changes in blood-pressure. Only minute quantities of intravenous pitocin are needed to induce labour, and this concentration is below the threshold required to cause an elevation of blood-pressure. Thus, provided other dangers can be avoided, an elevated blood-pressure is not a contraindication to the use of intravenous pitocin infusion in the induction of labour.

Reynolds *et al.* (1950) have demonstrated that intravenous posterior pituitary extracts are relatively ineffective in inducing labour unless combined with rupture of the membranes.

The common pathogens responsible for morbidity following rupture of the membranes are the anaerobic streptococcus and *Bacterium coli* (Lemmon, 1948). Large doses of penicillin are required to control the former, while the latter organism can best be eliminated by a mixture of sulphonamides or streptomycin. Carey, Charles and Hayes (1953) found that penicillin was the only antibiotic which reached the amniotic fluid in any appreciable concentration when administered to the mother by the usual routes (see Table I). For this reason, streptomycin is administered in a special way which will produce a very high concentration in the amniotic cavity and vagina after rupture of the membranes. Although soluble penicillin reaches the amniotic fluid when given by intramuscular injection at 6- to 8-hour intervals, it is more convenient to give this antibiotic with the streptomycin, thus saving the mother the discomfort of frequent injections.

If, after a short latent period, labour has not started, uterine activity can be stimulated by pitocin given in the effective and safe manner described below.

TABLE I

Penicillin Concentration at Time of Delivery Expressed in Bacteriostatic Doses in

Amniotic fluid	Cord blood	Maternal blood	Route of administration
256	64	32	1,000,000 units via polyethylene catheter into the amniotic cavity during the course of labour
			Time after I.M.I. 1,000,000 units
128		128	2 to 4 hours
128	4	16	6 hours
128	4	8	8 hours

Streptomycin Concentration at Time of Delivery Expressed in Bacteriostatic Doses in

Amniotic fluid	Cord blood	Maternal blood	Route of administration
64	16	32	1 g. via polyethylene catheter into the amniotic cavity during the course of labour
			Time after I.M.I. of 1 g.
Less than one	16	64	3 hours
Less than one	32	64	12 hours
Less than one	16	32	18 hours

Number of bacteriostatic doses recorded above is the reciprocal of the highest dilution (in nutrient broth) of the fluid under test which inhibited growth of the test organism, as judged by complete absence of turbidity after overnight incubation at 37° C. The "Oxford" strain of *Staphylococcus pyogenes* was used as test organism for the assay of penicillin concentration. For assay of all other antibiotics, a mutant of *Bact. coli* strain K 12 which requires threonine, leucine and thiamine (mutant W 677) was employed.

METHOD

A polyethylene catheter is sterilized by soaking for 18 hours in a 1 per cent solution of CTAB (cetyl-tri-methyl-ammonium bromide). This catheter is 1·5 m. long and 3 mm. external diameter, with its tip perforated on the side as well as being open at the end. It is introduced through a high puncture in the membranes into the amniotic cavity by means of a special introducer illustrated in Fig. 1. This instrument consists of a 5 mm. wide metal tube bent slightly like an S and has a stainless steel flexible stylette, the head of which is enlarged to almost the same size as the internal diameter of the tube. The stylette head is tapered to a blunt point. This instrument is modelled on the Drew-Smythe catheter but differs from it in having a wider bore which is uniform throughout the length of the instrument. The head of the stylette is modified

to compensate for these changes. The high puncture in the membranes is made by passing this introducer round the posterior aspect of the presenting part between the membranes and the uterine wall. The membranes are supported by the presenting part so that the blunt tip of the instrument will only rupture the membranes when it is passed above the presenting part to an area where the membranes have no underlying support. Usually this is in the neighbourhood of the neck of the foetus. The stylette is withdrawn and the polyethylene catheter threaded through the introducer. It enters the amniotic cavity with little resistance. The free end of the catheter is connected by means of a 3-way tap to an unbonded strain gauge or to an anaeroid type of sphygmomanometer, the catheter replacing the armband in this instrument. The third arm of the 3-way tap is connected by means of a standard blood transfusion giving set to a litre of sterile 5 per cent glucose in water to which 1,000,000 units of penicillin and 1 g. of streptomycin have been added (see Fig. 2). The fluid chamber of the unbonded strain gauge has a second opening into which is fitted a tap enabling air to be washed out of the system. The anaeroid sphygmomanometer can be readily fitted with a similar tap.

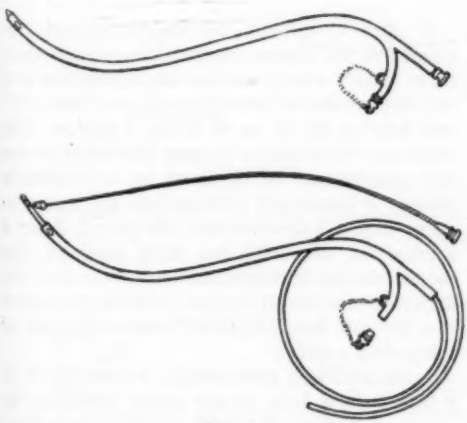


FIG. 1

The top portion of this diagram shows the metal introducer with the stylette in position. The lower part of the drawing shows the stylette withdrawn and the polyethylene catheter partly threaded through the introducer.

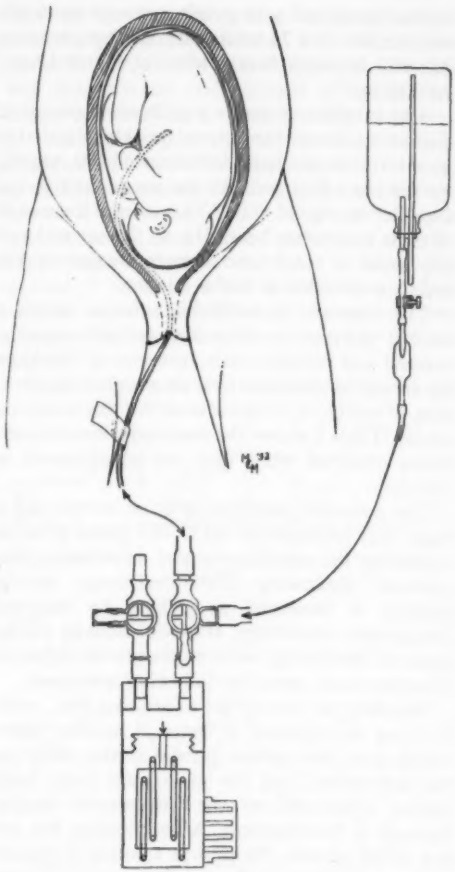


FIG. 2

Diagram of the polyethylene catheter passing through the high rupture in the membranes. The distal end is connected to a three-way tap, the second arm of which communicates with the reservoir of antibiotic solution and the third is fitted to the unbonded strain gauge.

The electrical output from the strain gauge is of the order of micro-ampères and is directly proportional to the fluid pressure. This output is amplified and fed onto a standard commercial continuous ink recording milliammeter. The paper in the recorder travels at the speed of ½ inch a minute. The recorder is fitted with

syphon pens and a large ink reservoir so that it will run for over 24 hours without any attention, one roll of paper being sufficient for 26 hours' recording.

The amplifier contains a calibration circuit so that its sensitivity can be very quickly adjusted to give a full scale chart deflection of 100 mm.Hg by the recording pen. As the paper used in the recorder is printed with 50 horizontal lines each of these represents 2 mm.Hg. In the vertical axis the paper is ruled into segments equal to the distance travelled in half a minute.

The reservoir of antibiotic solution serves a double purpose in that the catheter can be washed out intermittently, preventing blockage by vernix, at the same time as a high concentration of antibiotic is introduced into the amniotic cavity. Table I shows the concentrations of antibiotic obtained when they are administered in this way.

The patient is prepared with an enema and a bath, and occasionally oil is also given prior to rupturing the membranes and introducing the catheter. Following this interference uterine activity is increased as judged by external tocographic recordings. If uterine activity shows signs of decreasing, intravenous pitocin infusion is commenced, using the following technique.

Five units of pitocin are added to a litre bottle of 5 per cent glucose in water. A second bottle which does not contain pitocin is also hung on the drip stand, and the giving sets from both bottles connected to the intravenous needle through a Y-connexion. After washing the air out of the system, the pitocin solution is turned off and the plain glucose in water solution allowed to run during the venepuncture and the adjustment and strapping of the arm. When the patient is comfortable, the pitocin solution is started at the rate of 5 to 8 drops a minute. The record is watched closely for any undue prolongation of the contractions which are excited by the pitocin. The foetal heart rate is checked at regular intervals, especially if the intra-uterine pressure is elevated for more than 1½ minutes with a contraction. This method of recording uterine activity gives an accurate index of uterine tone. Normally, this is represented by a pressure of 8 to 12 mm.Hg between contractions, with the strain gauge at the level of the symphysis pubis.

If the duration of the contraction initiated by the pitocin is excessive, the drip is stopped immediately and the uterus will relax almost straight away. Fig. 3 shows an example of a prolonged contraction and elevated tone for 5 minutes due to excessive pitocin dosage. The foetal heart slowed during this period but returned to normal shortly afterwards.

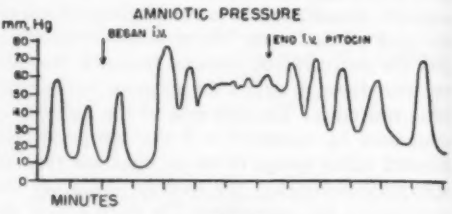


FIG. 3

This record shows the effect of an excessively high rate of intravenous pitocin administration. If, when an intravenous pitocin infusion is started, only one bottle is used and the drip rate is not adjusted before connecting the giving set to the needle in the vein, the above set of circumstances can readily develop. However, if an excessive amount is administered inadvertently, sufficient warning is given by the record to allow the drip to be stopped before serious foetal distress occurs. In the case illustrated above, there was only temporary slowing of the foetal heart rate.

If after 15 minutes the amplitude and frequency of the uterine contractions are less than those usually seen in normal labour the drip rate can be increased to 10 drops a minute, then to 15 and later to 20, 30 or 40 drops a minute. The response of the uterus to each increment in the drip rate should be observed for a 15-minute period. If prolonged contractions are going to occur they will do so within this period. After a satisfactory drip rate has been attained, the record should be inspected frequently and the drip rate checked at regular intervals to ensure that the rate has not altered with movement of the patient's arm.

In the case of a primigravida it may take 6 or 8 hours for a long closed unripe cervix to be taken up and reach 2 to 3 cm. dilatation. Frequently uterine activity dies down as soon as the pitocin infusion is stopped. This allows the patient to sleep during the night and work during the day.

Fig. 6A and Table II demonstrate that morphia has little depressant effect on the uterine activity induced by pitocin. It relieves both pain and apprehension and has proved a useful analgesic during pitocin inductions. If delivery occurred within 5 hours of administration of morphia, 1 mg. of N-allyl-nor-morphine was injected into the umbilical cord of the infant as soon as it was born and this counteracted the depressant action of the morphia on the respiratory centre of the baby.

Fig. 4 is an example of a para-1 who went out of labour following a surgical induction. Full cervical dilatation was accomplished under the action of intravenous pitocin.

Figs. 5 and 6 are records of a primigravida at 36 weeks by dates with a long unripe cervix who was stimulated into labour with intravenous pitocin. Once labour was established, the drip was discontinued and cervical dilatation continued spontaneously. This case was of interest in that initially she showed intolerance to 10 drops per minute of dilute pitocin but later, by gradually increasing the drip rate and allowing tolerance to develop, the incoordinate response was converted into a good pattern of activity. Maximum response was achieved by 60 drops a minute (5 units of pitocin to the litre) and no further increase in frequency or amplitude was obtained by increasing the rate to 140 drops a minute.

Table II is a record of uterine activity in a case

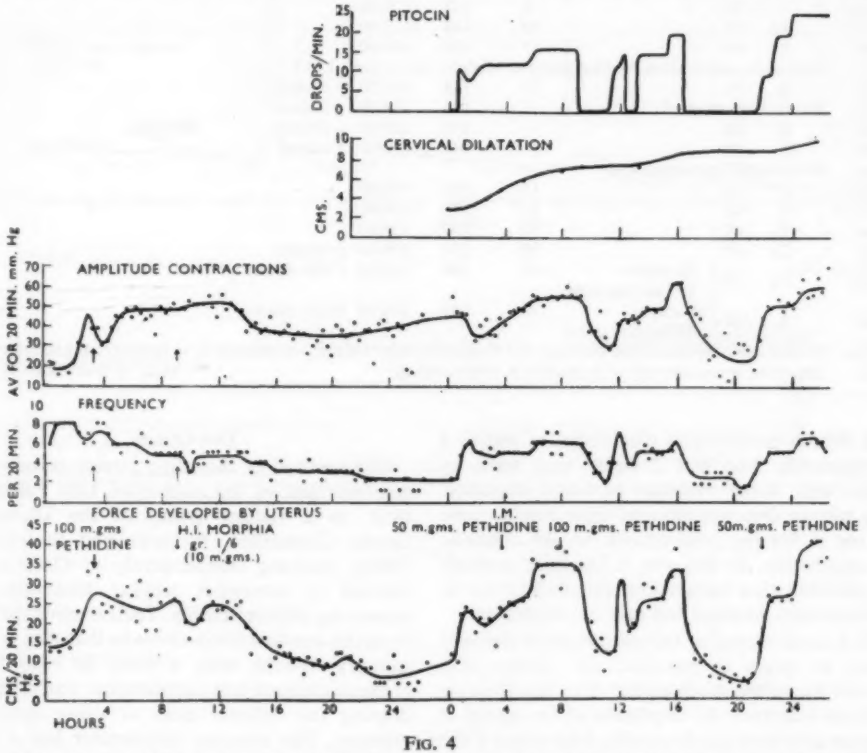


FIG. 4

Record of uterine activity throughout the labour of a para-1. The pitocin solution used in this case contained 10 units to the litre. Cervical dilatation was effected entirely by pitocin as, whenever the pitocin was stopped, uterine activity died down and further cervical dilatation did not occur.

TABLE II

Record of a breech delivery in a primigravida who was 2 weeks overdue by dates. A total of 7 units of pitocin was used. The drip was stopped before delivery to facilitate transfer to another delivery room. Normally, the drip should be kept going until the placenta is delivered and ergometrine has been given

Time after A.R.M. in hours	Minutes between apices of contractions	Amplitude of contractions in mm.Hg	No. of drops pitocin per min.	Foetal heart rate	Blood pressure	Cervical dilatation	Remarks
½	4½	40	—	150	120/74	Cervix ½" long	Painless contractions
3½	3	40	—	144	116/76		Commenced to feel discomfort with contractions
9	3	20	—	140	120/80	Cervix taken up	Intermittent backache only
12	8	20	—	144	120/80	Not dilating	Sleeping
19	12	10	—	140	120/80	Not dilating	
26	20	10	—	140	120/80	Not dilating	
27	Intravenous pitocin drip commenced						
27½	7	30	8	150	120/80		
27½	4½	40	20	148	120/80		
30	3	45	25	150	120/80		
31	Pain with contractions causing distress. Morphia gr. ¼ given I.M.I.						
32	3	55	23	148	120/70	½ dilated	
33	Pitocin drip stopped		—	144	120/70	½ dilated	
35	8	20	—	144	130/80	½ dilated	Sleeping
41	15	30	—	144	130/80	½ dilated	
43	Pitocin drip re-commenced						
43½	6	35	15	150	130/80		
44	6	40	22	136	130/80		
46	2½	45	30	140	130/80		
47	2½	45	30	144	130/80	¾ dilated	
48	1½	85 { 50 uterus 35 bearing down	45	144	130/80	Fully dilated	
49	2	160 { 60 uterus 100 bearing down	45	150	130/80	Fully dilated	
50	Pitocin drip stopped. Total duration of I.V. pitocin drip 12 hours—6 hours to ½, 4½ hours from ½ to full dilatation, 1½ hours second stage						
51	Delivered spontaneously of 6 pounds 5 ounces infant.						

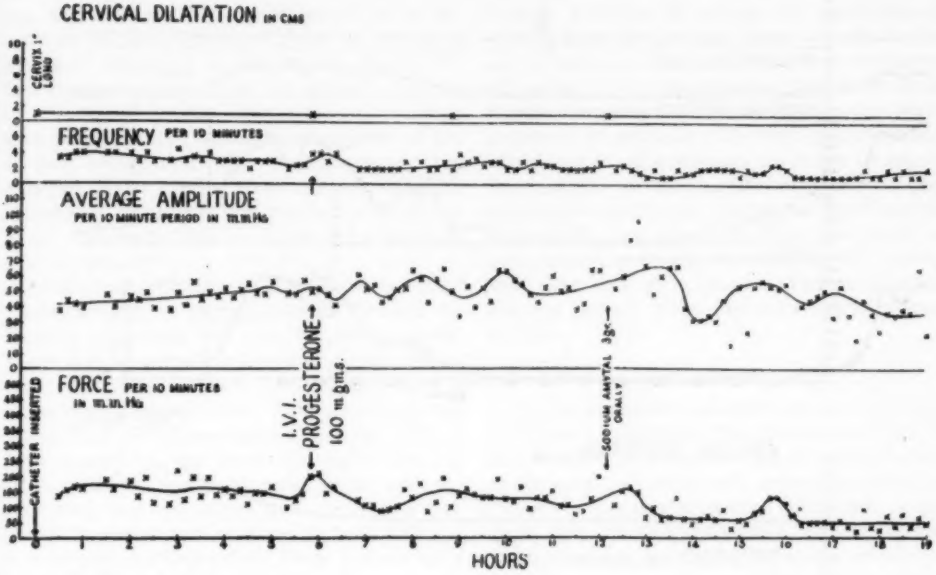
of a breech presentation with extended legs in a primigravida who was 2 weeks past term by dates with X-ray evidence of foetal maturity. The pitocin drip was stopped from time to time to see if uterine contractions would continue spontaneously. In this way it has been possible to establish that intravenous pitocin can on its own account produce full cervical dilatation.

If it is necessary to reduce induction delivery delay as much as possible, the pitocin drip should be started much earlier than was the case in these examples. By inspection of the record of uterine activity it can be readily determined if the frequency and amplitude of contractions are being maintained, and if this is not the case pitocin administration should be started.

DISCUSSION

This method of recording uterine activity was demonstrated by the author on 13th February, 1951, to a visiting group of the University Grants Committee. Williams and Stallworthy (1952), working independently at Oxford, developed a somewhat similar technique for measuring uterine activity. Their method differed from the one described above in that they used a mercury U-tube with a float to record the pressure changes and no provision was made for keeping the catheter clear or using antibiotic solution. The mercury manometer has a high degree of inertia, a considerable time lag and requires an appreciable fluid displacement for its operation. Although not as convenient as the

PARA 0 AGED 27 CASE No. 42.



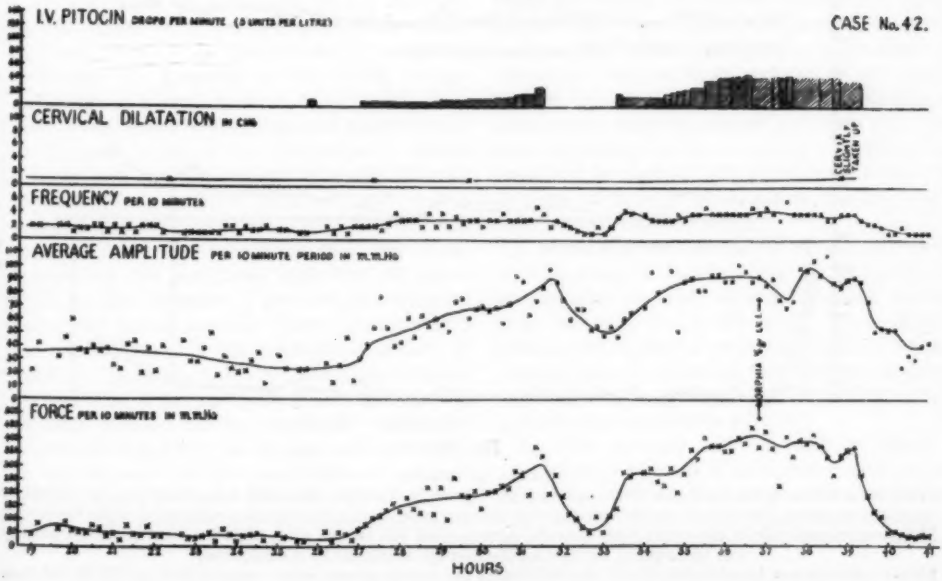
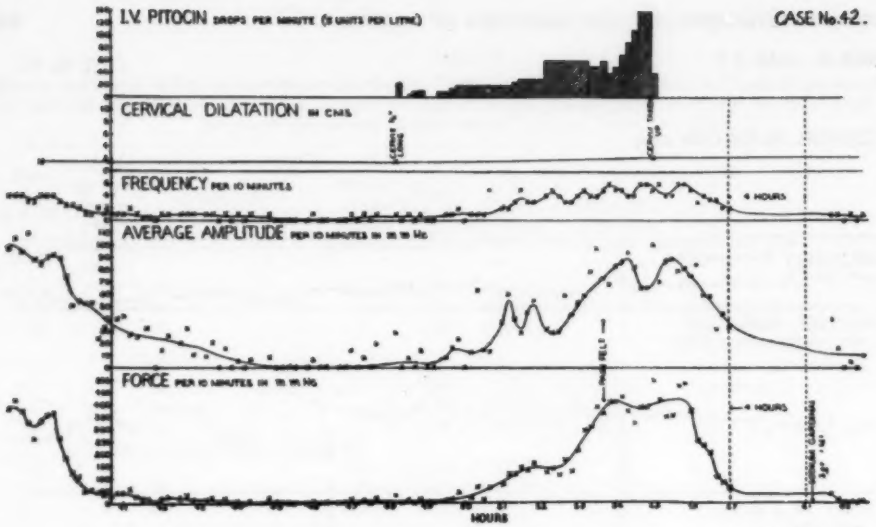

I.V. PITOCIN DROPS PER MINUTE (5 UNITS PER LITRE)
CASE No. 42.
CERVICAL DILATATION IN CMS
CERVIX TAKEN UP
FREQUENCY PER 10 MINUTES
AVERAGE AMPLITUDE PER 10 MINUTE PERIOD IN
MORPHIA
FORCE PER 10 MINUTES IN
HOURS

FIG. 6A


I.V. PITOCIN DROPS PER MINUTE (5 UNITS PER LITRE)
CASE No. 42.
CERVICAL DILATATION IN CMS.
FREQUENCY PER 10 MINUTES
4 HOURS
AVERAGE AMPLITUDE PER 10 MINUTES IN MM. HG.
FORCE PER 10 MINUTES IN MM. HG.
4 HOURS
HOURS

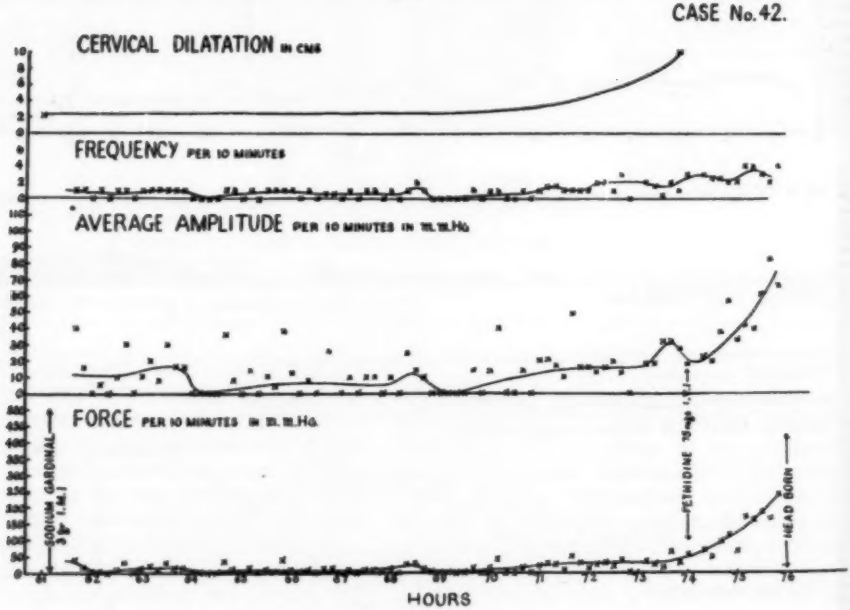


FIG. 6B

FIGS. 6A and 6B

Complete analysis of the same case illustrated in Figs. 5A and 5B. Cervical dilatation was determined by vaginal or rectal examinations. Number of contractions occurring in successive 10 minute intervals was recorded under frequency. The average amplitude of the contractions over the same periods was plotted next, while the force of uterine activity was obtained by multiplying the average amplitude by the frequency.

Pitocin administered intravenously had a dramatic effect on uterine activity while morphia (1/6 gr. I.V.I.) did little to depress this activity.

method described above, it is almost as expensive if a kymograph has to be purchased. While, with the mercury manometer method of recording, the errors are too large to permit its use for accurate research purposes, it can be used as a means of recording uterine activity during the first stage and monitoring the uterine response to intravenous pitocin. During the second stage this method overestimates the magnitude of the uterine contraction and underestimates the strength of the bearing down efforts, since the frequency response of the mercury manometer is not sufficiently high to follow these pressure changes accurately.

Alvarez and Caldeyro (1950) have recorded uterine activity by passing a needle through the anterior abdominal wall into the uterine cavity. More skill is needed to avoid important structures with this method than to introduce a catheter through the cervix. Patients usually will not tolerate the former method once the effect of local anaesthetic has worn off, while with the latter one the patients' movements are not restricted, they can change their position in bed, sit up for meals and washing and can sit on a bedpan without discomfort. These features have enabled records of the whole of the first and second stages of a number of labours to be obtained. The strain gauge tokodynamometer developed by Reynolds *et al.* (1948) is undoubtedly the best method of external tocography developed to date. External methods give an accurate index of the frequency of uterine contractions but the records of amplitude and tone are only relative and are not always accurate as will be seen from Fig. 7. The external methods have the advantage that the membranes are not punctured and they are more likely to give an index of the true physiological picture of uterine activity. These considerations are not important in the induction of labour. If internal methods initially stimulate uterine activity this is an advantage. In addition, the internal method allows amplitude of uterine contractions and tone to be measured accurately in mm.Hg and permits comparison of records from different patients. The accurate picture of uterine tone obtained with the internal methods is of the utmost importance in monitoring the response to oxytocics.

It has been found from experience that the volume of antibiotic solution run into the amniotic cavity has no effect on uterine tone or activity. Likewise the leakage of a small amount of fluid from the amniotic cavity after the initial loss of amniotic fluid is without further discernible effect on uterine activity. This is no doubt due to the postural adaptation which the uterus possesses, in common with other hollow viscera, allowing it to adjust its capacity to the volume of its contents. Although, following artificial rupture of the membranes, the amplitude of uterine contractions recorded has been as great as any occurring during the subsequent labour, they have been quite painless. The contractions become painful when cervical dilatation commences.

Summary

(1) An improved technique for the induction of labour is described. This method permits the maintenance of a high antibiotic concentration in the amniotic cavity and vagina, reducing the danger of infection of mother and foetus, at the same time as the hydrostatic pressure in the amniotic cavity is recorded by means of a polyethylene catheter introduced through the cervix at the time the membranes are ruptured. In cases where uterine activity shows evidence of subsiding after artificial rupture of the membranes, pitocin is administered by continuous intravenous infusion and the optimum safe drip rate ascertained in each case by observing the record of uterine activity. Used in this way the dangers of pitocin which other workers have encountered can be avoided.

(2) The internal method of recording uterine activity which is described has the advantage of convenience to both obstetrician and patient over methods previously used. The patients tolerate the technique very well, and it allows an accurate record of uterine tone and contractions to be made in absolute units facilitating comparison from patient to patient.

(3) This method can be used to effect a vaginal delivery even in primiparae with unripe cervices some weeks before term. This technique is applicable also to cases of toxaemia who up to the 36th week have been controlled by bed rest and ion exchange resins.

Acknowledgments

I am indebted to Mr. C. D. Read and Professor J. C. McClure Browne for facilities and encouragement in carrying out this work and to the Wellcome Research Institution for a grant towards the cost of the recording apparatus and for a supply of N-allyl-nor-morphine. I am grateful to Professors N. J. Eastman of Johns Hopkins Hospital and University, George Corner of the Carnegie Institution of Washington, Curtis Lund of Rochester, N.Y., Howard Taylor of Columbia University, R. A. Woodbury of the University of Tennessee, R. Torpin of the University of Georgia and Paul Bruns of the University of Colorado for hospitality in their departments where some of the work was carried out during a year spent in North America on a University of London Postgraduate Travelling Fellowship. I am especially indebted to Professor S. R. M. Reynolds of Johns Hopkins University and the Carnegie Institution of Washington for his close collaboration in some of this work and for the opportunity of gaining experience with the TKD method of recording uterine activity.

Mr. B. J. O'Connor of the Biophysics Department of the Postgraduate Medical School, London, has been responsible for the design and construction of the A.C. amplifier used with the unbonded strain gauge.

Mr. Quilley of Evershed and Vignoles Ltd., London has been very helpful in supplying the recording milliammeter used in this work.

This work could not have been carried out without the co-operation and interest of the nursing staff of the delivery floor at Hammersmith Hospital.

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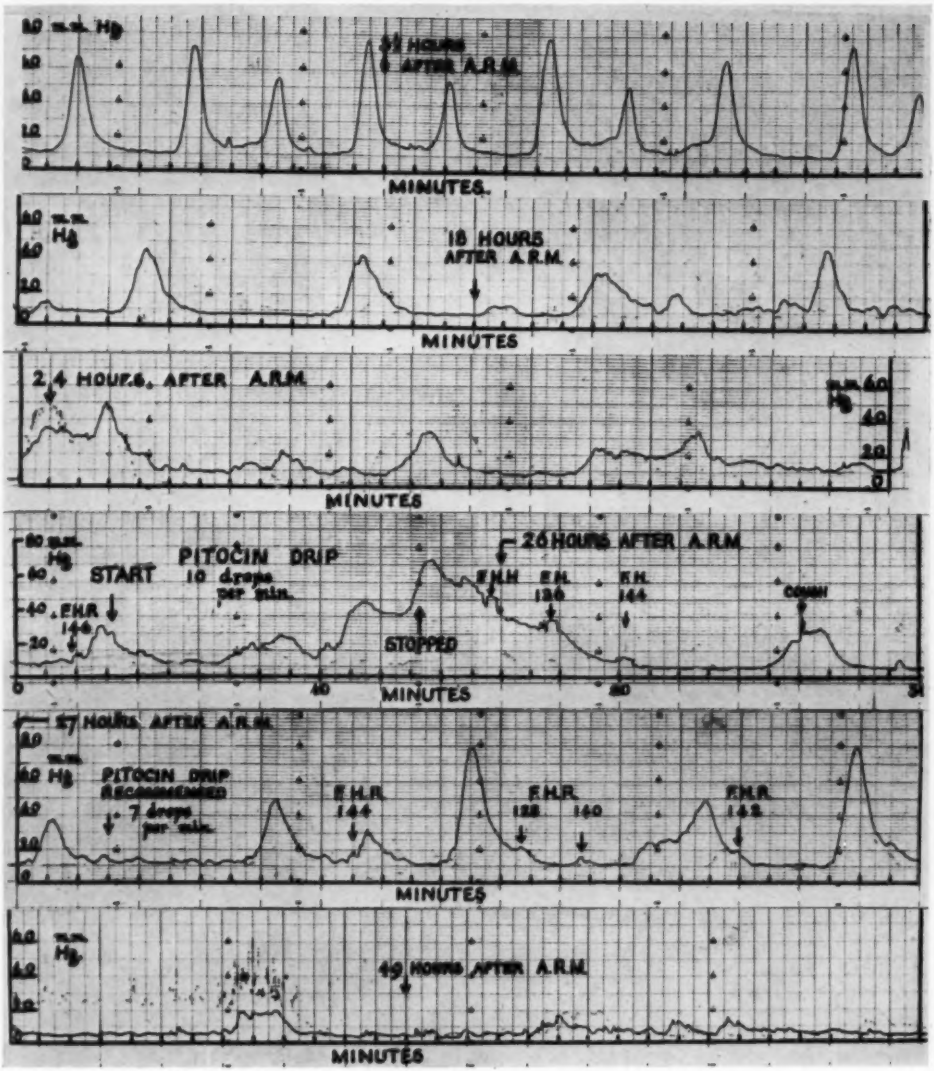
MINUTES
18 HOURS AFTER A.R.M.
MINUTES
2,4 HOURS AFTER A.R.M.
MINUTES
START
PITOCIN DRIP
10 drops per min.
STOPPED
26 HOURS AFTER A.R.M.
F.H.R. 144
F.H.R. 136
F.H.R. 144
COUGH
MINUTES
27 HOURS AFTER A.R.M.
PITOCIN DRIP RECOMMENCED
7 drops per min.
F.H.R. 144
F.H.R. 128
F.H.R. 140
F.H.R. 142
MINUTES
49 HOURS AFTER A.R.M.
MINUTES

FIG. 5A

H.M.C.

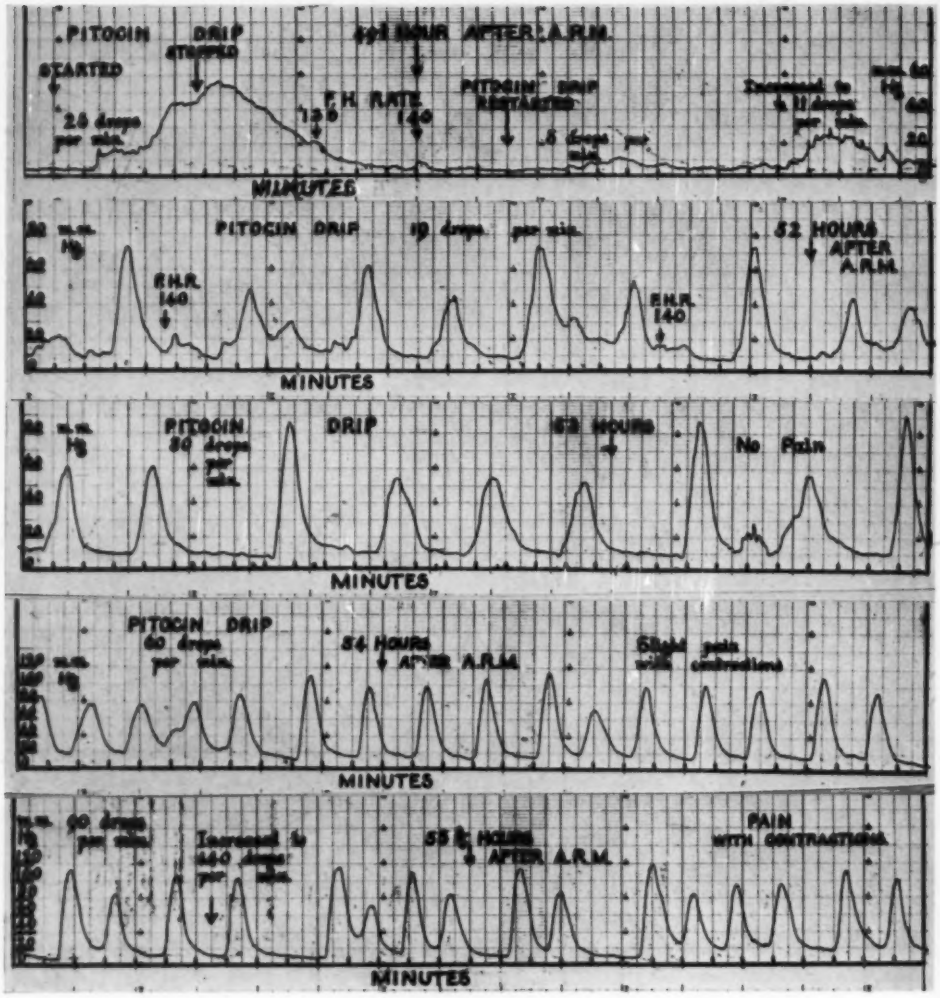

FIG. 5B

FIGS. 5A and 5B

Records of uterine activity of a primigravida with a long unripe cervix, who was induced at 36 weeks on account of pre-eclampsia (Case No. 42). Following artificial rupture of the membranes, uterine activity gradually decreased and became irregular and incoordinate.

When the pitocin drip (5 units per litre) was first started at 10 drops a minute, a prolonged contraction occurred. An hour later, the drip was restarted at 7 drops and gradually increased to 25 drops a minute. After a control period, intolerance was shown to 25 drops a minute, but by reducing the drip rate to 5 drops and later increasing it the incoordinate pattern was corrected and optimal activity was obtained with 60 drops a minute. Further increases in rate up to 140 drops were tried without obtaining any additional uterine activity.

The intra-uterine pressures developed by this patient after artificial rupture of her membranes were amongst the highest recorded in a series of 60 cases. The pressures developed during the administration of 60 drops of pitocin solution a minute were considerably higher than those developed during a normal labour in a primipara.

H.M.C.

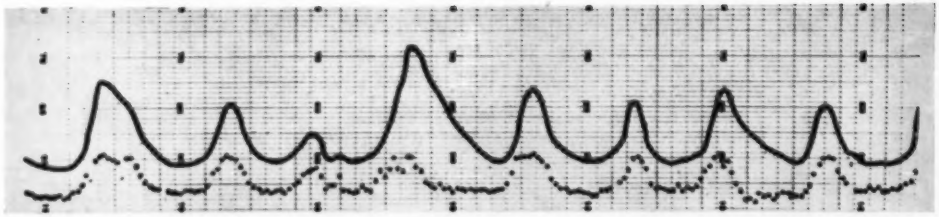

FIG. 7

Amniotic fluid pressure is shown as a continuous line. The dotted line is a record made simultaneously with the TKD (external strain gauge tokodynamometer) located over the upper segment. Although the intra-uterine pressure during different contractions varied, the amplitude recorded by the TKD remained fairly constant.

SOME MANCHESTER PIONEERS IN OBSTETRICS AND GYNAECOLOGY*

BY

JOHN WEBSTER BRIDE, M.D., B.S., M.D., F.R.C.O.G.

Late Lecturer in Systematic Obstetrics and Gynaecology, University of Manchester, Hon. Consultant Gynaecologist, United Manchester Hospitals and the Manchester Northern Hospital

THE invitation to deliver this, the 7th William Meredith Fletcher Shaw Memorial Lecture, has given me great pleasure and I thank you Mr. President and the Council for the honour conferred by you, especially as I am the first Manchester gynaecologist to give this lecture, emanating, as it does, from Manchester.

My association with St. Mary's Hospital, Manchester, began overy forty years ago, and about that time I came into possession of McClintock's "Smellie's Treatise on Midwifery", which whetted my appetite to explore the past of the hospital and the contributions made by the members of its staff to the advancement of obstetrics and gynaecology. Since then Miles Phillips's *William Smellie and the Maternal Mortality Problem* in 1933, and R. W. Johnstone's *William Smellie, the Master of British Midwifery*, published in 1952, have sustained my interest in obstetrical history. In the following brief sketches I have outlined the work of some of the prominent surgeons, who have practised obstetrics and gynaecology in Manchester since the middle of the eighteenth century, and I have taken the title of my lecture from them.

Arthur Burgess of Manchester, delivering the Hunterian Oration of 1941, remarked that he was the first Hunterian orator to be an entirely provincial surgeon, and that he was having, as it were, a provincial's "day out". I expect that, after listening to me, you will agree that I am having a provincial gynaecologist's "day out".

CHARLES WHITE, F.R.S., 1728-1813

The tree of obstetrics in Manchester was planted by Charles White, and that this root was sound is proved in the branches since put forth from that tree. White was born in Manchester in 1728. His father, Thomas White, also practised in Manchester, and was probably the first to perform and record a case of Caesarean section in England and Wales before 1740. Charles White was a very prominent figure in the life of Manchester, inspiring admiration in his professional brethren, and not a little awe in the lay mind. Thomas De Quincey, who wrote the confessions of an English opium-eater in 1821, in his autobiography mentions White on several occasions as by far the most eminent surgeon in the North of England. White's life has been fully and ably written by Cullingworth, to whose work I am indebted for most of the facts concerning him. His public services to his city are notable for the leading part he took in the foundation of the Manchester Infirmary in 1752 when he was 24 years of age, and also at the age of 62 years in founding the Manchester and Salford Lying-in Charity in 1790.

He was a life-long friend of John Hunter, and with him attended the lectures in London of John Hunter's scarcely less celebrated elder brother, William Hunter.

White was elected a Fellow of the Royal Society in 1762 in his thirty-third year and I quote from Cullingworth the copy of his certificate of candidature dated 19th November, 1761. It reads:

> "Mr. Charles White, surgeon at Manchester, who some time ago communicated two chirurgical papers to the Society, being

* The William Meredith Fletcher Shaw Memorial Lecture delivered at the Royal College of Obstetricians and Gynaecologists on 16th October, 1953.

> desirous of the honour of being a Member of the Royal Society, we recommend him on our personal knowledge as a gentleman, by his skill in his profession and extensive practice, well qualified, and likely to become a useful member."

Six names of prominent citizens of Manchester are appended to this, and amongst them that of John Byrom, the writer of the poem from which the hymn "Christians awake" is an extract.

On the day of his admission as a fellow of the Royal Society, White was also admitted as a member of the Corporation of Surgeons, now the Royal College of Surgeons of England.

White's published writings amount to twenty-four. His *magnum opus* published in 1773 was *A treatise on the management of pregnant and lying-in women, and the means of curing, but more especially preventing the principal disorders to which they are liable*. It was an immediate success, and ran into four English editions, in addition to an American one, and translations into French and German.

In his interpretation and management of puerperal sepsis White showed himself well ahead of the times. He recognized the contagiousness of the disease, its relationship to surgical infection and the importance of cleanliness and fresh air. He emphasized the value of the sitting-up posture on the first day after delivery, as illustrated in his treatise. A. H. Curtis of Chicago writes in his system of obstetrics and gynaecology "the credit for postural surgical drainage has been accorded to George Ryerson Fowler, and in surgical literature the position is widely known as the 'Fowler position' . . . In strict priority, however, this position involving the drainage principle should be known as White's position." White also recognized the possible septicity of the lochia, and recommended the injection of antiseptics into the uterus.

In 1784 White published *An Inquiry into the nature and cause of that swelling in one or both of the lower extremities, which sometimes happens to lying-in women*; and this was probably the first work on this subject written in England. However, in 1800 Hull published his book entitled *An Essay on Phlegmatia Dolens* in which he disagreed with White's views, and was the first to so designate this condition. White in 1801 replied to the criticisms and enlarged Hull's suggestion into "Phlegmasia Alba Dolens".

It was Charles White's proud boast, that in all the sixty years he had practised no woman whom he had delivered had died of puerperal fever.

The value of his work is illustrated by the fact that Boër, who became Professor of Midwifery in Vienna in 1789, and had learned White's methods in England, introduced them in Vienna with the result that in 65,000 cases, over a period of thirty years, the mortality was only 1·3 per cent. When Boër was deposed in 1822 and replaced by his assistant Klein, who discarded White's methods, the mortality in his first year was 7·8 per cent rising to 29·33 per cent.

In White's outside interests was the study of anthropometry. He wrote one of the most important papers in the literature of that subject —"An account of the regular gradation in man, and in different animals and vegetables, and from the former to the latter", which he read to the Literary and Philosophical Society of Manchester in the year 1795. A criticism in the *British Medical Journal* of 31st October, 1903 speaks of White as the "Father of Anthropometry".

As was to be expected of a friend of John Hunter he made a museum, which was unfortunately destroyed by fire in St. Mary's Hospital, Manchester, where it was housed. He was man-midwife extraordinary to that charity for 21 years, retiring in 1811. He died in 1813 at the age of 85 years after a life devoted to the advancement of the knowledge of obstetrics.

John Hull, M.D., 1761-1843

John Hull, a contemporary and friend of Charles White, was born at Poulton-le-Fylde on 30th September, 1761. At 16 years of age he served an apprenticeship to Dr. Lancaster of Blackburn, and after passing his examination at Surgeon's Hall in London in 1784, and obtaining the degree of doctor of medicine in Leyden, he came to Manchester in 1796, where he practised until the date of his retirement in 1837. Perhaps Hull was not so eminent a man as Charles White, but he certainly approached him closely. He was undoubtedly a very capable

obstetrician and a highly educated man well versed in languages, Latin, Greek, French, German, and Italian, and he was a very able writer. His public services to Manchester included his hand in the foundation of the Manchester Institution for Curing Diseases of the Eye, now the Manchester Royal Eye Hospital, in 1814, and in 1819 he helped to establish the Lock Hospital. He was the founder of the Manchester Medical Society and its first President in 1834. In June 1804 Hull joined the staff of the Manchester and Salford Lying-in Hospital, now St. Mary's Hospital, and in 1805 was appointed to the senior post of physician, all the other members of the staff being called men-midwives in ordinary or extraordinary—titles not altered until 1828 when they became surgeons. He retained this post until his retirement.

Hull's most notable contribution to medical literature was his *Defence of the Caesarean Operation*. The operation had been condemned as unjustifiable by Mr. Wm. Simmons, Senior Surgeon of the Manchester Infirmary, but Hull easily got the better of his feeble and illogical arguments. Like Charles White, Hull also wrote on the swelling of the patient's legs during the puerperium in an essay *On Phelgmatia Dolens including the Symptoms, Causes, and Cure of Peritonitis Puerperalis and Conjunctiva* in 1800, and he was the first to apply the term "Phlegmatia dolens" to the condition. He also found time to publish in 1801 a translation of *Two memoirs on the Caesarean operation* by the great French obstetrician, J. L. Baudelocque. In the *Philosophical Transactions of the Royal Society of London* for 1787, Mr. John Hull, "gentleman-midwife", reported a case of quintuplets delivered by him. "Two living children survived the birth but a short time. The mother, in spite of the crowds with which her chamber was continually filled, continued to recover and was able to be out of bed on her third day." By way of a hobby he published *Elements of Botany* in 2 volumes, Manchester 1800.

Brockbank says: "Hull, by his writings on the subject, established the necessity of Caesarean section in certain abnormal conditions of the pelvis, and thus helped Thomas Radford and his immediate successors at the Lying-in Hospital to put it on a sure foundation among the recognized operations of surgery. Certain principles and reasons for doing the operation as bearing on the relative value of the life of the mother and child, which he gave, are still regarded as sound."

Radford says that Hull was a regular attender at the Established Church and distinguished for his correct and religious conduct. He died in 1843, aged 81 years.

Thomas Radford, M.D., F.R.C.P.(Edin.), F.R.C.S.(Eng.), 1793-1881

Thomas Radford, a contemporary of Hull and Charles Clay, was born in Manchester in 1793, and like most others of his time he started life in general practice. He was appointed man-midwife for out-districts to the Manchester Lying-in Hospital in 1818, and was successively man-midwife in ordinary, surgeon extraordinary, and consulting physician. He became Chairman of the Board of Management in 1874, holding this position until his death in 1881 at the age of 87. He left to St. Mary's Hospital, Manchester his museum with its unique collection of deformed pelves now housed in the University of Manchester, and also the Radford library of 3,400 volumes. This was later catalogued by Cullingworth and contains many valuable old books. It has been transferred to the University of Manchester.

Radford was President of the Manchester Medical Society in 1848. He delivered in 1854 the first address ever given on obstetrics before the Provincial, now the British Medical Association, on Caesarean section. He was an early advocate of abdominal section and a loyal supporter of Charles Clay in his ovariotomies at a time when much courage was needed to side with him.

Radford was a hard worker and an indefatigable writer, and he lectured far and wide on the subjects of craniotomy and Caesarean section. His principal publication was *Observations on Caesarean Section, Craniotomy, and on Other Obstetric Operations*, 1st edition 1865, 2nd edition 1880, London.

In 1843 he delivered a course of lectures to

members of the profession, published in the *Provincial Medical and Surgical Journal*, now the *British Medical Journal*, and in the *British Record of Obstetric Medicine and Surgery* edited by Charles Clay. In this course he strongly denounced craniotomy as an operation of election, and recommended it to be performed generally as an operation of necessity.

Radford in his book carried his investigations on the treatment of contracted pelves up to 1880. At that date he recorded 77 cases of Caesarean section in England, Scotland and Ireland, but no case from Wales. Of this number 55 happened in England, of which the large number of 25 occurred in the neighbourhood of Manchester. The mortality was then 80 per cent.

When Eardley Holland in 1921 carried out his collective investigation into Caesarean section performed in Great Britain and Ireland from 1911-1920, it was my good fortune to be asked to supply him with the figures from Manchester, which amounted to 648 of his 4,000 cases, and with a mortality of 2 per cent.

In order to complete the statistics of Caesarean section in Manchester, I published in 1951 the results of operations from 1875 to 1920, the year of Holland's investigation. This showed, over a period of 46 years, a mortality of 6 per cent. In 1948 the mortality for the operation in cases of contracted pelvis was 0 per cent in St. Mary's Hospital, Manchester.

Radford's work was doubtless inspired by Hull and especially his efforts towards reducing the incidence of craniotomy as an operation of election. He described experiments with wooden blocks devised as follows: "The pelvis of Elizabeth Thompson is in the museum of St. Mary's Hospital, Manchester and was presented by me. There is a block of oak carved on the model which, with others, I have given to the aforesaid hospital. However, it is one thing to operate on an inanimate machine, a block of wood, let it be ever so accurately formed, and another to operate on the pelvis of a living woman. I deny the possibility of bringing a mutilated full-grown child through such a pelvis, whatever appliances are used." Radford attributed the bulk of Caesarean fatalities to protraction of labour: "In one case 12 days, one 7 days, one 6 days, so that death cannot truly be attributed to the operation." He attributes peritonitis to sloughing of the cervix and vagina, and lays stress, as did Amand Routh in 1911, on the fact that "Frequent examinations per vaginam are productive of very serious mischief. These results are attributable to frequent and unwarrantable interference." He cites the successful cases of ovariotomy of Charles Clay of Manchester as a parallel in some sort to the Caesarean operation, as to the nature of the operation and the risks incurred.

In 1921 Holland concluded, with regard to the safest material for suturing the uterine wound, that silkworm gut was the best, silk the next best and catgut the most unsuitable material. It is of interest that Radford says: "Suture the uterus with silver wire, never use catgut as the knots become untied, the wound opens, and the patient dies." Munro Kerr at the same meeting described "The Lower Uterine Segment Incision in Conservative Caesarean Section". We know now that this method is the answer to the question and not the type of suture material. McIntosh Marshall of Liverpool finds that the first lower segment operation was performed in 1805 by F. B. Osiander and reported by him.

I quote the concluding remarks in Radford's book: "It now only remains for me to bring forward my proposition first made in 1843. Deep reflection since that period, and a strong sense of humanity, have induced me to further declare that the Caesarean section should be generally performed as an operation of election, and that craniotomy should be as far as possible abolished, and ought only to be performed in a very few cases, notably when the child is dead. I am quite aware that many of the opinions I have so urgently stated in the foregoing remarks are at variance with those of the profession generally; yet they have been most conscientiously advocated. They originated from the dictates of humanity to try to extinguish as far as possible that dreadful expedient—nay shall I not call it that murderous operation? Craniotomy."

Much credit must be given to Radford for his consistent and persevering advocacy of Caesarean section, when the mortality was so high. One wishes he could see the present day results, towards which it must be allowed his contribution was great.

Charles Clay, M.D., L.R.C.P.(Edin.), Extra L.R.C.P.(Lond.), 1801-1893

Charles Clay was born at Bredbury in Cheshire in 1801 and educated in Edinburgh, where he qualified as a licentiate of the Royal College of Surgeons. Early in life he was apprenticed to Mr. Kinder Wood, surgeon-in-ordinary to the Manchester Lying-in Hospital, and attended his lectures at the Pine Street School of Medicine, founded in 1825 by Thomas Turner, F.R.C.S., at which time John Dalton, of Atomic Theory fame, was lecturer in Pharmaceutical Chemistry there.

Clay settled in Manchester in 1839 and he was appointed to the staff of St. Mary's Hospital in 1857, where he was also lecturer in midwifery.

In 1842 he performed his first ovariotomy, removing a tumour weighing 36 pounds. In 1865 he published an account of 111 cases of ovariotomy, 77 of them successful, the mortality being 30·6 per cent. Clay says the name ovariotomy had been suggested to him by Sir James Y. Simpson. His first twenty-two cases were performed without an anaesthetic and he always used the large incision from sternum to pubes. In 1863, before the Obstetrical Society of London, Clay recorded the first successful case of hysterectomy in Europe. In 1848 he edited *The British Record of Obstetric Medicine and Surgery* and was its chief contributor, and in 1870 he published *A complete Handbook of Obstetric Surgery*.

In the time at my disposal I must leave much unsaid, especially as Sir William Fletcher Shaw, in his Presidential Address to the Manchester Medical Society in 1951, has given an exhaustive account of Clay's life and works and especially of his controversy and the libel action with Spencer Wells. He was generally regarded the world over as "the Father of Ovariotomy in England", and Fehr of Heidelberg calls him the original hero of that operation. Peaslee in *Ovarian Tumours*, New York, 1872, says "to Dr. Clay of Manchester, however, more than to all other operators, belongs the credit of having placed the operation on a sure foundation". Peaslee also says "His experience in midwifery counts up to twelve thousand cases. He has been second to none in the knowledge of all subjects allied to this operation, having had twenty-five hundred volumes on obstetrics alone for reference in his own library, and which he has donated to the Manchester Medical Society and the London Obstetrical Society. Though now over seventy years of age, he still wields the pen or the scalpel, as circumstances require, and has never confined his cutting to the latter only."

Clay died at Poulton-le-Fylde in 1893 aged 92 years.

David Lloyd Roberts, M.D.(St. Andrews), F.R.C.P., F.R.S.(Edin.), 1835-1920

Lloyd Roberts was born in Stockport in 1835. After a hard struggle in early life he managed to acquire the means to educate himself, and he received his early medical training at Mr. Turner's Pine Street School of Medicine in Manchester. Incidentally this was the first complete medical school in the provinces, and in recognition of this it was granted the Royal patronage in 1836, thereupon becoming the Manchester Royal School of Medicine and Surgery. In 1872 this was incorporated with Owens College and was thus the nucleus of the Medical School of the University of Manchester. He also studied at the Manchester Royal Infirmary and in London.

Lloyd Roberts became honorary surgeon to St. Mary's Hospital, Manchester in 1858, a position which he occupied for 62 years until his death in 1920. In 1885 he was appointed honorary gynaecologist to the Manchester Royal Infirmary, and he was lecturer in clinical obstetrics and gynaecology in the University of Manchester. He was Vice-President of the Obstetrical Society of London, President of the Manchester Medical Society in 1873 and President of the North of England Obstetrical and Gynaecological Society in 1892, 1905 and 1907.

It is regrettable that he did not publish the results of his work, as in his early days he was under the influence of Charles Clay, was a good surgeon and from the year 1858 until 1874 had practically the whole of the abdominal work of St. Mary's Hospital in his hands. The mortality ranged from 20-30 per cent and Lloyd Roberts alone kept the flag flying for ovariotomy in Manchester. He made two valuable contributions to literature: "Religio Medici" by Sir

Thomas Browne, a Revised edition, edited by himself in 1898, and "The Scientific Knowledge of Dante" in 1914.

Lloyd Roberts left a large fortune and of it a sum of money the income thereof to provide an honorarium in payment each year of lectures to be delivered in Manchester and London. This bequest has been of great value to obstetrics and gynaecology from the variety of subjects chosen and the eminence of the lecturers. Some have given good descriptions of the founder of the lectures, and of these the fullest and most pleasant to read is "Victorian Doctor" by J. Johnston Abraham in the Lloyd Roberts Lecture delivered before the Medical Society of London in November 1948.

At this point it is remarkable to note that the preceding five gentlemen's ages totalled 430 years, headed by Charles Clay at 92, and tailed by John Hull at 81 years, an average life of 86 years, pointing to the toughness of these "Lancashire Lads" in spite of hard work.

Charles James Cullingworth, M.D., F.R.C.P., 1842-1908

Cullingworth was born in Leeds in 1842. He was appointed to the staff of St. Mary's Hospital, Manchester in 1874, and became Professor of Obstetrics and Gynaecology in the University in 1885.

He was elected a Fellow of the Royal College of Physicians in 1887, and he was the first obstetric physician to read the Bradshaw lecture, his subject being "Intraperitoneal haemorrhage incident to ectopic gestation". In 1888 he was honoured by an invitation to join the honorary staff of St. Thomas's Hospital, London, and was appointed obstetric physician there, a post which he held until 1904. During the last two years of his life he was editor of the *Journal of Obstetrics and Gynaecology of the British Empire*.

His fame as a gynaecologist rests mainly on his work *Clinical Illustrations of the Diseases of the Fallopian Tubes and Tubal Gestation*. His advocacy of removal of diseased tubes and ovaries led to a storm of protest from the leaders of the Obstetrical Society of London, but Cullingworth held to his views in spite of harsh criticism, and in the course of a few years the surgical methods advocated by him were established on a firm basis. His first six operations on inflamed tubes and ovaries were carried out in St. Mary's Hospital, Manchester.

It is to Cullingworth that Manchester owes the best biography of Charles White.

William Japp Sinclair, M.A., M.D., M.R.C.P., 1846-1912

Sinclair was born in 1846 and educated at the Aberdeen Grammar School and Aberdeen University. He came to Manchester in 1873, in due course was appointed physician to the Manchester Southern Hospital, and in 1906 became a member of the staff of St. Mary's Hospital when the two amalgamated. To the end of his days he was more a literary man than a practical surgeon. Throughout his life he was a fighter and the stormy petrel of Manchester gynaecology. He succeeded Cullingworth as Professor in 1888, occupying the chair until his death in 1912. He was the terror of students and hardly a fair examiner, insisting on his own views being given in papers and viva voce to the exclusion of all others. Sinclair was the, first professor of obstetrics to insist on his students having a compulsory period of residence in a maternity hospital for 3 months later reduced to 1 month. Sir John Stopford, the present Vice-Chancellor of our University, was in the first group in 1910 who took the 3-months' course. Sinclair was a prolific writer especially on uterine cancer, gonorrhoea, vaginal hysterectomy, ventral fixation, and Caesarean section.

He was a great admirer of Semmelweis and published in 1909 *Semmelweis, His Life and His Doctrine*. J. George Adami, delivering the first Lloyd Roberts Lecture in 1921, chose as his subject "Charles White and the arrest of puerperal fever", in which he supported White's views, and opposed Sinclair's claims for Semmelweis, that puerperal fever was not contagious, but an intoxication set up by decomposed animal matter and only conveyable from one puerperal woman or cadaver to another. Yet a year later Arnold Lea, Sinclair's assistant Lecturer, published his valuable monograph "Puerperal Infections" in 1910, in which he showed that the studies on streptococci and their relationship to puerperal fever have solved the problem of the aetiology of the disease. Adami

considered that Sinclair was a striking example of that common tendency to exalt the work of the foreigner at the expense of the honest pioneer labour of one's own countrymen. He ignored the work of Ould, Denman, White and Kirkland, among whom White assuredly had first place. Actually Semmelweis did no more than reintroduce the British methods pursued by his predecessor Boër. Harvey Graham, in his book *Eternal Eve*, gives an excellent account of the work of Semmelweis. Through Sinclair, as its principal promoter, there originated in Manchester the *Journal of Obstetrics and Gynaecology of the British Empire*, the first number appearing in 1902. This was indeed an invaluable contribution to the advancement of obstetrics and gynaecology the world over. He conceived the idea of the North of England Obstetrical and Gynaecological Society. The first meeting was held in 1890, and Sinclair was the first general secretary and framed the rules. He was a strong supporter of the first Midwives' Act and a member of the first Board.

Sinclair was one of the early successful performers of Caesarean section and published in the *Lancet* of 1901 a series of ten successful cases of Caesarean section. In 1907, in the *Journal of Obstetrics and Gynaecology of the British Empire*, he reported a Caesarean section performed for the fourth time on the same woman. This record has since been broken by Fletcher Shaw who carried out the operation for the seventh time, using catgut suturing of the uterus on each occasion. This case was reported by him in the *Journal of Obstetrics and Gynaecology of the British Empire*, 1921.

Sinclair was an ardent politician in the Conservative cause in South Manchester, and it was for these services, as much as for his work as an obstetrician, that he received the honour of knighthood in 1904.

Archibald Donald, D.L., M.A., M.D., F.R.C.P., LL.D.(Hon.), F.R.C.O.G.(Hon.), 1860-1937

Donald was one of the pioneers of modern gynaecology and one of the most beloved men in his profession. Born in 1860 and educated in Edinburgh he was a true son of Scotland, although he always acknowledged that it was in Manchester that he learned his clinical work, and first shouldered responsibility, having been the resident obstetric officer at St. Mary's Hospital for three years. Soon after Cullingworth was appointed to the staff of St. Thomas's Hospital, London in 1888, Donald filled his vacancy on the staff of St. Mary's Hospital, Manchester, and was also Honorary Gynaecological Surgeon to the Manchester Royal Infirmary from 1895 to 1919. Manchester being the centre of a large industrial population employing much female labour, prolapsus uteri abounded in the area, and there Donald did his greatest pioneer work, for he developed the operation of colporrhaphy, and his introduction of catgut suturing contributed much to its success. Unfortunately he did not write much about the operation, so that his name was never attached to what he created some twenty years before Fothergill joined the staff of St. Mary's Hospital, Manchester. Much of the credit went to Fothergill, who modified the operation and it was known by his name for a time. It remained for Fletcher Shaw to settle the question by calling this colporrhaphy the Manchester operation in the *American Journal of Obstetrics and Gynecology* for 1933. Donald was also an early writer in 1922 on endometriosis or adenomyoma. As an exponent of the clinical side of obstetrics and gynaecology he held a position second to none in this country and no man was more successful in practice or achieved better operative results.

In spite of the calls of such a practice he yet found time to influence the obstetrical and gynaecological thought of his day. He was Professor of Systematic Obstetrics and Gynaecology in the University of Manchester in 1912, and Clinical Professor in 1920 until his retirement in 1925. He was responsible for the inclusion in the final M.B., Ch.B. Examination of a clinical examination in obstetrics and gynaecology.

Many honours came to him and for his services in the R.A.M.C. during the 1914-1918 war he was made a Deputy Lieutenant of Lancashire. He was a past president of the Obstetrical Section of the Royal Society of Medicine in 1926-27, of the North of England

Obstetrical and Gynaecological Society, and of the Manchester Medical and Pathological Societies. His old University of Edinburgh conferred upon him an honorary LL.D. and he became in 1934 an Honorary Fellow of the Royal College of Obstetricians and Gynaecologists, of which he was a strong supporter and a member of its first Council.

He served on the Departmental Committee of the Ministry of Health, which reported upon the cause and prevention of Puerperal Sepsis; and in the celebration of the centenary of the Coombe Lying-in Hospital, Dublin he gave an address on "Antiseptics and Asepsis in Midwifery". Among his numerous publications one of the most refreshing is *The Transition*, a retrospect of thirty years' experience in his subject.

He had all the attributes which attract the love and admiration of junior colleagues, and many had and have reason to be grateful for his helping hand.

In private life he was hospitable to a degree, delightful to play golf with owing to his quiet sense of humour, and above all he loved his fellow men.

William Edward Fothergill, M.A., B.Sc., M.D., 1865-1926

Fothergill came of Quaker stock and, although born in Southampton in 1865, was of Yorkshire descent and received his early education in Darlington. After a brilliant career at Edinburgh University he took the degrees of M.A., B.Sc. and M.D.

He obtained his first gynaecological appointment in 1899 at the Manchester Northern Hospital, and also became Director of the Clinical Laboratory of the Manchester Royal Infirmary. This latter post he held for six years, and it accounted for his sound knowledge of pathology. He joined the staff of the Manchester Southern Hospital in 1904, and, on the amalgamation of the hospitals, the staff of St. Mary's Hospital, Manchester being senior surgeon at the time of his death in 1926. He held the first appointment of Honorary Assistant Gynaecological Surgeon to the Manchester Royal Infirmary from 1908, and became Honorary Surgeon in 1919 until 1925.

In the University he was appointed in 1920 Professor of Systematic, and in 1925 Professor of Clinical Obstetrics and Gynaecology. By many generations of students he will be remembered as one intensely interested in their work and play, and he was an ideal chairman of a smoking concert. Fothergill exercised a profound influence on British obstetrics and gynaecology. He had strong views on most subjects and the power of expressing them forcibly. He was a prolific writer. His *Manual of Midwifery* in 1896 was a popular text-book in many teaching centres and reached a fifth edition. His *Manual of Diseases of Women* in 1910 introducing pathological classification was an original contribution to the text-books of the period.

Finally he did much to popularize the operation of colporrhaphy introduced many years previously by Donald. In many lucid papers, Fothergill advocated this method of treatment for uterine prolapse, and introduced a modification of the older operation, so successful that for a time his name became associated with it, though now it is usually called, as advocated by Fletcher Shaw, the Manchester operation. At the first British Congress of Obstetrics and Gynaecology held at Birmingham on June 3rd and 4th, 1921, Fothergill read a paper "The End Results of Vaginal Operations for Genital Prolapse". At the Queen's Hospital, Birmingham he also demonstrated the technique of his colporrhaphy operation upon a case of genital prolapse, at which I assisted him.

I will digress awhile and say that the *Journal of Obstetrics and Gynaecology of the British Empire*, Volume 28, 1921, opens with a foreword by Comyns Berkeley and Eardley Holland on the rebirth of the Journal after the lapse of publication during the war years 1914 to 1918, in which they ask for the support necessary to justify the steps taken.

There is no need to emphasize the gratitude to the Journal of all engaged in our specialty, but especially of all of us younger men, who had been on active service and quite out of touch with our subjects.

This volume, I always think, is of peculiar value. In the first place it records fully the proceedings of the *First* British Congress of Ob-

stetrics and Gynaecology, and it also contains the enormous amount of information on Caesarean section gathered by Eardley Holland and Munro Kerr.

It is interesting to look forward thirty years from its pages, where can be noted in the list of Abstracters in Birmingham for the Review of Current Literature the name of an energetic young gynaecologist, Hilda N. Shufflebotham, to be found in 1951 occupying the Presidential Chair of our College as Dame Hilda N. Lloyd.

Again there is an article by S. D. Clippingdale "The Accouchement of Queen Jane Seymour", who possibly was delivered by Caesarean section in giving birth to King Edward VI. Henry VIII is reported to have said on this occasion "Save the life of the child for another wife can easily be found". Thirty years after this publication Holland chose as his subject for this lecture "The Princess Charlotte of Wales. A Triple Obstetric Tragedy."

Lastly, there appears "Reminiscences of Lawson Tait" by Christopher Martin in 1920, and again in thirty years Fletcher Shaw places Charles Clay of Manchester in true perspective.

To return to Fothergill, his manner of speech was simple and direct, his humour broad and sometimes Rabelaisian.

On 4th November, 1926, after making a characteristic after-dinner speech at the Manchester Glasgow University Club he sat down, and within a few minutes passed away. Few men have done so much to spread abroad the fame of the Manchester School.

DANIEL DOUGAL, *M.C.*, M.D., F.R.C.O.G., 1884-1948

Daniel Dougal was born in Strathaven, Lanarkshire, in 1884, and as his father, a general practitioner, soon afterwards left Scotland, his education was obtained, and the whole of his professional life was spent, in the University and the hospitals of Manchester. So it is that with Manchester his name will always be linked.

An association that was to last for his lifetime commenced when he came to St. Mary's Hospital, Manchester in 1909. He joined the North of England Obstetrical and Gynaecological Society in 1913, and published his first paper in the *Journal of Obstetrics and Gynaecology of the British Empire*, the subject being "A new form of Pelvigraph".

In 1914 he served with the 52nd Field Ambulance in France being appointed to the staff in 1917 when he became D.A.D.M.S. to the 34th Division. He was awarded the Military Cross, Croix de Guerre with Palms, and was twice mentioned in despatches.

He occupied the chair of Systematic Obstetrics and Gynaecology from 1927 to 1943, and was Director and Professor from 1943 until his death in 1948. Dougal organized and expanded the existing facilities for teaching, and developed the museum with a fully documented catalogue.

In addition to his appointment at St. Mary's Hospital he was Honorary Gynaecological Surgeon to the Manchester Royal Infirmary, and excelled as a Clinical Teacher. His *Lecture Notes for Students* (6th Edition 1937 rearranged as an uncompleted Edition in 1944) were a model. They were issued privately, and were the basis of his text-book, almost ready for publication when he died in 1948.

He was unfailing in his attendances at the North of England Obstetrical and Gynaecological Society's meetings, and he was President, and for many years acted as Treasurer. During his membership of the Gynaecological Visiting Society he only missed two meetings from 1921 until his death.

He was a director of the *Journal of Obstetrics and Gynaecology of the British Empire*, and latterly was chairman of the Editorial Committee.

Dougal was invited to America in 1937 to deliver the Joseph Price Oration, taking for his subject "The Problem of Endometriosis". He was chosen to represent British gynaecology at the International Congress at Amsterdam in 1938, when he read one of the principal papers on "The Aetiology of Thrombosis and Embolism".

He was a foundation Fellow of the Royal College of Obstetricians and Gynaecologists, an Honorary Fellow of the Edinburgh Obstetrical Society, and an Honorary Fellow of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons. He was President of the Manchester Medical Society in

1947 when he gave his last address, entitled "From the Foetal Point of View", and he was then a very sick man.

Dougal had an infinite capacity for work and was a great organizer. His contributions to his subject covered every field and he was accepted as an authority both at home and abroad. His interest in the teaching and welfare of students was intense, and several generations of students held him in esteem and affection. Although he never claimed priority for himself in any sphere of activity yet he was, as Leyland Robinson so aptly wrote at the conclusion of Dougal's obituary, one of the best "all rounders" of his age and generation.

Conclusions

In assessing the value of the contribution of these men of the Manchester school to the advancement of the knowledge of obstetrics and gynaecology a high place may justly be given to their share in placing the Caesarean operation on a sure foundation through the efforts of Charles White, Hull, Radford, and later of Sinclair.

Charles White by his early recognition of the nature and treatment of puerperal fever and thrombosis, followed by Hull and in more recent times by Arnold Lea and Donald, did pioneer work.

Cullingworth, in the face of great opposition, established surgical methods for the treatment by removal of diseased tubes and ovaries.

Charles Clay of Manchester is now generally recognized as "the Father of Ovariotomy in England".

The credit of establishing a satisfactory colporrhaphy operation for the cure of prolapsus uteri must largely go to Donald and Fothergill, and indeed A. J. Wrigley in his Refresher Course on Prolapse in the *British Medical Journal* of 4th April, 1953, says "Many and varied have been the operative procedures suggested for the cure of prolapse. Only one has stood the test of time, and that is the operation first evolved at the beginning of the century by the surgeons in Manchester, notable among whom were Donald and Fothergill".

To Sinclair, as its original promoter, obstetrics and gynaecology owe the Journal of the British Empire, one of the most important of its kind in the world. He also founded the North of England Obstetrical and Gynaecological Society.

Dougal raised the standard of teaching in his subjects, and greatly increased the credit of the Manchester School both at home and abroad.

These men had vision, and they were fearless in expressing their views. Their efforts were directed towards alleviating the suffering of women in child birth, and curing the diseases incidental to their sex. They rendered good service to our special branch of medicine, and I have welcomed the opportunity for this endeavour to keep their memory green.

I gratefully acknowledge the valuable help received from my colleagues at St. Mary's Hospital, Manchester, and also from Mr. G. Wilson, Librarian to the Medical Library of the University of Manchester. I am indebted to Mr. Frank Dale for his help in the preparation of the lantern slides illustrating my lecture.

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ADENOCARCINOMA OF THE VAGINAL VAULT FOLLOWING GESTATIONAL HYPERTROPHY OF THE CERVIX UTERI

BY

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IN a previous communication (Martin and Kenny, 1950) a case of gestational hypertrophy of the cervix uteri simulating adenocarcinoma in 2 successive pregnancies was described. Total hysterectomy with excision of a wide vaginal cuff was carried out at the conclusion of the second pregnancy. Two years and 3 months after this operation the patient again presented herself with true adenocarcinoma of the vaginal vault.

As the present attitude towards equivocal or borderline cancer in pregnancy appears to be conservative, the case is thought worthy of further report. The history, presented in more detail in 1950, is as follows.

A woman aged 32 years was referred to this hospital in the 28th week of her third pregnancy, in 1947. A small pedunculated polyp was avulsed from the posterior lip of the cervix at the 24th week and had been reported as adenocarcinomatous. The patient was transferred to us for Wertheim's hysterectomy.

The cervix was inspected under anaesthesia and appeared entirely normal. Biopsies were taken from the anterior and posterior lips of the cervix, in the region of the adenosquamous junction. These pieces of tissue and the section of the original polyp were submitted to Professor Dible, Director of the Department of Pathology of the School.

The polyp and the section of the posterior lip showed an identical appearance of a malignant-looking epithelium without any sign of invasion of the stroma (Fig. 1). The biopsy from the anterior lip showed the change to a lesser degree. The pathological reports are presented in the earlier paper.

The sections were submitted to several eminent pathologists and their views were divergent. The weight of opinion favoured expectant treatment, and this was decided upon.

A further biopsy was taken from the posterior lip of the cervix, which still appeared healthy, at the 36th week. The hypertrophic change was present to an even more marked degree, but still without any sign of invasion of the stroma. It is perhaps significant that at the end of his report on this section Dr. B. Lennox commented: "It is difficult now to avoid calling it adenocarcinoma."

A healthy child was delivered by elective classical Caesarean section during the 37th week. Biopsies were taken from the anterior and posterior lips of the cervix 6 weeks after delivery. Histological examination showed a completely normal cervix, the growth that had been present during pregnancy having now completely disappeared. The cervix was inspected 5 months and 12 months after delivery, and was entirely normal. The patient was most anxious to have another child, and, because of the apparently complete resolution of the lesion we then felt it would be safe for her to do so.

In September, 1949, she reported to hospital, then 8 weeks pregnant. The cervix was softened and appeared healthy. The vaginal cytology was normal.

She continued to attend at regular intervals and the vaginal cytology was studied after each visit. This continued to be normal until the 24th week, when Dr. Erica Wachtel reported a group of cells that were suspicious, although the cervix had appeared normal. The patient then defaulted until the 31st week, when she was persuaded to enter hospital and was examined under anaesthesia. The cervix was darkly purple and a very large friable polyp, resembling a branch of cauliflower, was attached by a slender

base to the right posterior adenosquamous junction of the cervix. The polyp filled the vagina, and had a stalk about ½ cm. in diameter. Its surface was vascular and friable. The polyp was completely excised and the bleeding controlled by mattress sutures.

The histology of the tumour was identical with that of the polyp and biopsies in the previous pregnancy. There was no sign of invasion of the stroma and the base was healthy. The pregnancy continued without incident, and the vaginal cytology thereafter was normal.

The woman and her husband desired that sterilization be carried out and so, taking into consideration the previous classical section, the bizarre and possibly malignant lesion of the cervix, and the increasing reluctance of the wife to attend hospital regularly, a Caesarean hysterectomy was planned.

This was carried out during the 37th week. A cuff of vagina was removed with the cervix, but the normal-appearing ovaries were preserved. A healthy child was delivered, and the convalescence was normal.

The uterus was preserved as a museum specimen. The whole adenosquamous junction of the cervix was covered with warty polypi. A sagittal section was cut through the length of cervix and there was no sign of invasion.

It may be stated here that many of those closely connected with the case considered that the treatment adopted had been unnecessarily radical, and we were rather forced to justify the operation on the strength of the patient's temperament. This was such that any chance of a regular, prolonged follow-up was remote.

Subsequent History

The woman was seen 7 weeks and 6 months after the operation. She was well and there were no symptoms, the pelvis was normal on examination, and the vaginal cytology negative. She was asked to return in a further 6 months. This appointment was not kept, and she was finally traced to a district far from the hospital. She wrote to say that she was completely well, that domestic commitments prevented her from making the journey, but she would attend her local doctor regularly. This was unfortunately agreed to.

Present History

On the 23rd July, 1952, 2 years and 3 months after the total hysterectomy, she was sent to hospital by her doctor with a history of vaginal bleeding for about a month.

On questioning, she admitted to slight post-coital bleeding for about a year, a heavy yellow discharge for 10 weeks, and bouts of bright red vaginal bleeding for about 6 weeks. She had not sought advice before because "hospitals always made her feel depressed". The bleeding at its worst had necessitated the use of two vulval pads a day.

She would admit to no other symptoms. The general health was excellent, she was full of energy, and had not lost weight. There had been no pain. The appetite was excellent and the bowels moved normally without pain. There was no cough or sputum, and no urinary symptoms. She had not experienced hot flushes. The records showed that her weight had increased since 1949.

Examination

The patient appeared healthy and well-nourished. She was afebrile and the pulse rate was 68 per minute. General examination was negative. There were no palpable lymph glands and no oedema of the ankles was detected. The blood-pressure was 136/86.

The abdomen showed only the healthy scar of the previous operation. There was no mass, tenderness, or free fluid and the liver and spleen were not palpable.

The external genitalia were normal.

Speculum Examination

The vaginal vault showed a ragged necrotic ulcer rather more than 1 inch in diameter situated to the right side. A similar but much smaller ulcer was present on the left side. The ulcers were friable and free contact bleeding was demonstrated.

Palpation showed the bases of the ulcers to be indurated, the induration extending for a short distance beyond the ulcer edge. Slight thickening extended from the larger ulcer into the right parametrium. The vaginal vault was otherwise freely mobile and descended slightly when the patient coughed. Digital examination through

the rectum confirmed the presence of a limited area of induration in the region of the vaginal vault. The rectal mucosa was not affected and there was no suspicion of abnormality elsewhere in the pelvis.

A piece of the necrotic material was removed with ring forceps and preserved for histological examination.

On the 28th July, 1952, the patient was admitted to hospital. The haemoglobin was 13·7 g. (92·5 per cent). The blood sedimentation rate was 12 mm. in the first hour and the blood urea 25 mg. per cent.

A chest X-ray and catheter specimen of urine were normal. Dr. C. V. Harrison reported on the tissue removed as follows: "This biopsy shows a columnar cell papillary tumour exactly like that of the first biopsy and that, which occurred in the last pregnancy. Histologically the 3 tumours are indistinguishable."

It was felt that the condition was now undoubtedly malignant and that treatment should be instituted at once without waiting for the result of a biopsy from the edge of the tumour. Because of the comparatively localized nature of the growth it was decided that radiation was the treatment of choice in the first instance.

On the 31st July, under anaesthesia, cystoscopy, sigmoidoscopy, multiple biopsies of the vagina were taken and a first radium insertion was performed.

Examination confirmed the previous findings, except that the induration extended out into the right parametrium for about 1 inch. Cystoscopy and sigmoidoscopy showed no lesion. Several large biopsies were taken from the growing edge of the tumour, and the first radium application inserted.

Histology of first biopsy (by Dr. I. Doniach):

"The biopsies consist of dense connective tissue with a squamous covering. In a number of places this covering has been replaced by the same tumour which has been described previously. Much of the tumour projects as a papillary growth from the surface. There are areas, however, where fairly extensive carcinomatous invasion has occurred into the connective tissue" (Figs. 2 and 3).

Second and third radium applications were given, and at the third application the ulcers were less indurated and there were definite signs of healing.

Histology of biopsy taken at the third radium insertion (Dr. A. Pearse):

"Sections of these biopsies do not contain any viable tumour."

The patient remained entirely well throughout the treatment. After the radium insertions a course of deep X-ray therapy was begun, and the patient was discharged from hospital on the 31st July, 1952, to continue treatment as an outpatient.

The very serious nature of the condition has been explained to the patient and she has reluctantly consented to attend hospital at regular intervals. Apart from a mild adhesive vaginitis, which subsided completely, there has been no reaction to the treatment. When last seen in May 1953, she was well, the weight was increasing and there were no symptoms. Marital relations had been re-established without difficulty, pain or bleeding.

Examination showed the vaginal vault to be healed, supple and mobile. There was no parametrial induration. The vaginal cytology has remained negative.

Comment

It would be convenient to regard this as a case of mistaken diagnosis, a condition frankly malignant from the beginning. The facts make this difficult to substantiate. The polyp avulsed during the first observed pregnancy and repeated random biopsies taken from normal-appearing cervix, showed the picture of adenocarcinoma, but without invasion. Further random biopsies taken a few weeks postpartum presented an entirely normal histological picture. Novak and Rutledge (1948) have referred to the "irreversible somatic mutation which transforms a normal epithelial cell into a cancer cell". Here was a condition which, at least in the first instance, was apparently reversed.

The adenosquamous junction of the cervix, which was the original site of the dubious growth, was removed, together with a cuff of

vagina. Thus it seems unlikely that the later invasive lesion was a recurrence.

It therefore remains to consider the condition a re-occurrence in a new site, an example of cancer-proneness, or the remains of unsuspected invasive malignancy in an earlier growth.

Danforth (1950) and Hertig (1951) have advised, from considerable observation, that the attitude to equivocal or borderline cervical cancer during pregnancy should be particularly conservative. Though in all probability this case is a rarity, it does emphasize the importance of an adequate and prolonged follow-up of all cases of so-called gestational hypertrophy.

Summary

The history of a parous woman, who had changes in the cervix uteri closely simulating adenocarcinoma in 2 successive pregnancies, is described. Invasiveness could not be demonstrated on either occasion, and the cervix in the intervening months was histologically normal.

A Caesarean total hysterectomy with excision of a wide vaginal cuff was carried out at the end of the second observed pregnancy. Contact was lost with the patient 8 months after this operation. Two years and 3 months after the operation she again presented herself with a frank adenocarcinoma of the vaginal vault.

The relationship between the growths is briefly discussed.

I am indebted to Professor J. C. McClure Browne and Mr. Ian Donald for permission to publish this case, and to Dr. C. V. Harrison and his colleagues of the Department of Pathology for their advice and criticism. I would also like to express my thanks to Dr. Lilian Walter of the Department of Radiotherapy for her courteous co-operation.

The photomicrographs are by Mr. E. V. Willmott, F.R.P.S., F.I.B.P.

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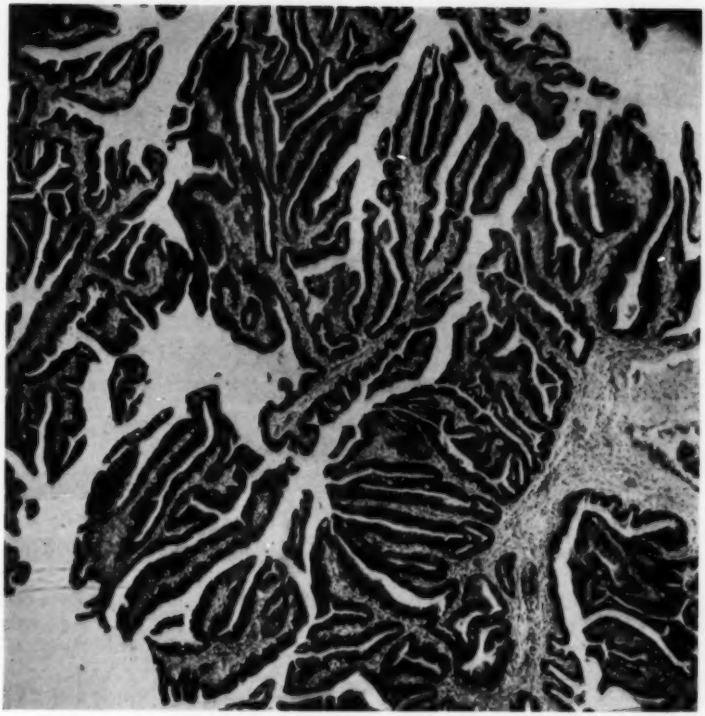

FIG. 1
Cervical polyp removed at 24th week of 1st observed pregnancy (1947). ×40.

R.T.M.

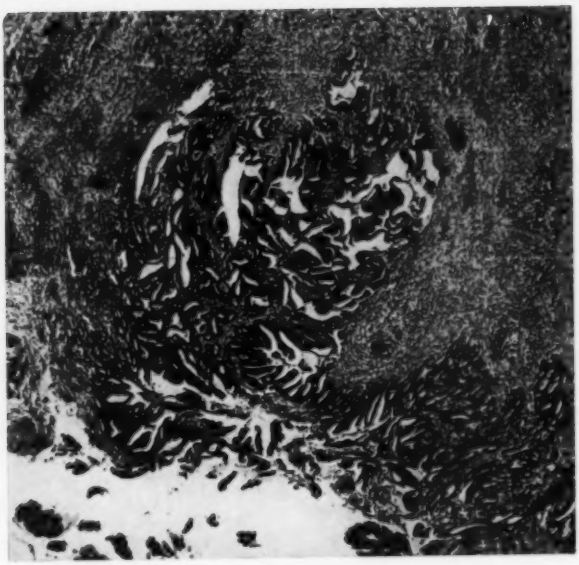

FIG. 2

Biopsy of vagina showing carcinomatous invasion. ×40.

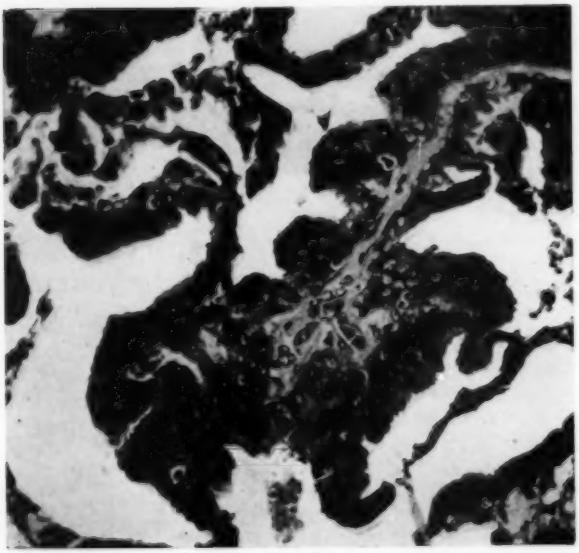

FIG. 3

As Fig. 2. ×380.

R.T.M.

THE APPEARANCES OF LIPOID IN THE CELLS OF THE VAGINAL SMEAR OF THE GUINEA-PIG

BY

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THE present research was designed to study the distribution of lipoid in the cells of the vaginal smear and to compare these results with the appearances in the cells of the smear of the spayed animal after treatment with oestrogen.

MATERIAL AND METHODS

Smears were taken from 24 virgin guinea-pigs using the technique of Selle (1922). The animals were aged between 9 months and 1 year and were known to have a regular oestrous cycle of 16-17 days. The smears were dried in the air, fixed in 10 per cent formalin, washed in distilled water then 50 per cent alcohol. They were then stained with Sudan III for 5-10 minutes, decolourized in 50 per cent alcohol and washed in distilled water. Haematin was used as a counterstain. High concentrations of alcohol were avoided as these may dissolve some of the lipoid (Kaufmann and Lehmann, 1929; Romeis, 1929). Sections of the vaginal wall were also made from 6 virgin guinea-pigs during the period of oestrus. The sections were cut at 10μ thick and stained with Sudan III and haematin.

For the experimental part of the investigation 8 ovariectomized guinea-pigs aged about 1 year were used. In each case 1 month was allowed to elapse after ovariectomy to ensure complete recovery from the operation and the disappearance of ovarian hormones from the blood. Five of the animals then received 0·1 mg. oestradiol monobenzoate intramuscularly daily for 6 days and vaginal smears were taken during the 5th and 6th days of the oestrogen treatment. The remaining 3 animals were used as controls; they received no hormone and from each sections were made of the vaginal wall. The smears and the sections were stained with Sudan III and haematin.

RESULTS

There is a considerable choice of terms to denote the sexual cycle and its various stages in the guinea-pig. The cycle is divided into the dioestrous or quiescent period during which the vagina is closed and the oestrus or period of sexual activity when the vagina is open. There are 4 stages of oestrus determined by examination of the vaginal smear and those described by Bacsich and Wyburn (1939), with which we agree, are adhered to in this account.

The lipoid appearances observed are the following:

NORMAL ANIMALS

First Stage of Oestrus. The smears show large irregular nucleated epithelial cells. Most of these contain coarse lipoid droplets which vary in size, some being very large; they are distributed irregularly throughout the cytoplasm (Fig. 1).

Second Stage. The smears show a preponderance of cornified cells and some irregular nucleated epithelial cells. Both types contain numerous fine lipoid droplets which are mostly uniform in size and, in some cases, almost obscure the nucleus (Fig. 2).

Third Stage. The smears show numerous rounded epithelial cells, a decreasing number of cornified cells and some leucocytes. These epithelial cells are derived from the deeper layers of

the vaginal epithelium. They contain a relatively small amount of fine lipoid droplets and in many of the cells lipoid is absent (Fig. 3). In some of the smears there remains a nest of epithelial cells belonging to the first stage of oestrus and in these the lipoid droplets are large and of varying size.

Fourth Stage. The smears show a decreasing number of rounded epithelial cells and numerous leucocytes. No lipoid was noted in the epithelial cells (Fig. 4).

The lipoid appearances in the wall of the vagina are in agreement with the above findings in the smears. Fig. 5 shows the lipoid appearances in the vaginal wall at the first stage of oestrus. The superficial cells contain coarse droplets of lipoid and are in the process of being shed; they are identical with the cells of the smear seen in the first stage (Fig. 1).

Experimental Animals

The smears from the animals which received oestrogen showed mostly epithelial cells of the type seen in the first stage of oestrus, and all these cells contained coarse lipoid droplets of varying size. No lipoid was observed in the sections of the vaginal wall of the control animals.

Discussion

The above findings suggest that the shedding of the vaginal epithelium at oestrus is a process of fatty degeneration. The amount of lipoid is greatest in the superficial cells during the first and second stages of oestrus when the epithelium is at its maximum thickness. In the third stage the epithelial cells contain only a small amount of lipoid and this is absent from the deepest epithelial cells which are shed at the fourth stage.

The fact that the intense appearances are seen in the cells furthest from their main blood-supply suggests that the presence of the lipoid is due to lack of oxygen. This is in agreement with the views of the pathologists (Boyd, 1947) on the causes of fatty degeneration. It is also supported, to some extent, by the results of Clark and Clark (1940) who reported that in the living rabbit the formation of fat in the subcutaneous tissue tended to diminish during a period of active circulation and to increase again with the return of quiet circulation. The nutrition of the superficial cells when the epithelium is at its maximum thickness may also be diminished by the concomitant oedema in the vaginal wall which accompanies the general congestion of the whole genital tract at oestrus. The above findings in the normal animals are in agreement with those of Trilby (1943).

The present results also demonstrate that the lipoid appearances are under oestrogen control and can be reproduced experimentally.

Summary

1. In the normal guinea-pig numerous lipoid droplets are demonstrated in the cells of the vaginal smear during Stages I and II of oestrus. These become diminished during Stage III and are absent during Stage IV.

2. Lipoid is also demonstrated in the cells of the vaginal smear in double ovariectomized animals treated with oestrogen and was found to be absent from the vaginal epithelium in the control animals.

3. The shedding of the vaginal epithelium at oestrus appears to be a process of fatty degeneration.

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FIG. 1

Photomicrograph of vaginal smear from normal virgin guinea-pig at Stage I of oestrus. The shed epithelial cells mostly show coarse droplets of lipoid which appear black in the photomicrograph. Stained Sudan III and Haematin. ×475.

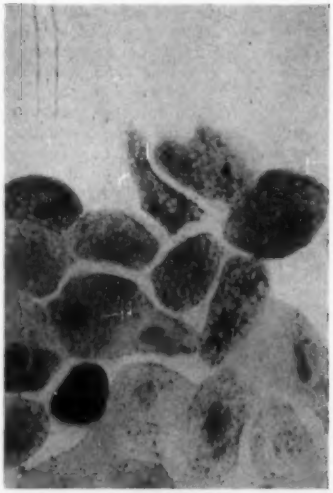

FIG. 2

Photomicrograph of vaginal smear from normal virgin guinea-pig at Stage II of oestrus. The smear shows mostly cornified cells and some nucleated epithelial cells. Both contain numerous fine lipoid droplets which appear black in the photomicrograph. Stained Sudan III and Haematin. ×475.

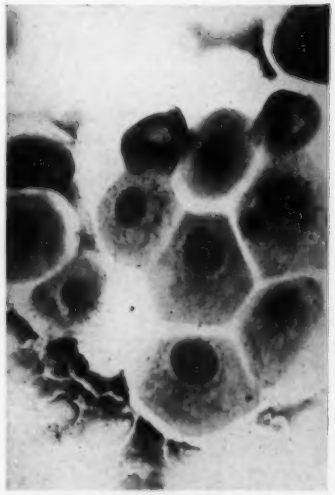

FIG. 3

Photomicrograph of vaginal smear from normal virgin guinea-pig at Stage III of oestrus. The smear shows numerous rounded epithelial cells which contain a small amount of fine lipoid droplets. The lipoid appears black in the photomicrograph. Stained Sudan III and Haematin. ×475.

T.N., R.S.S.

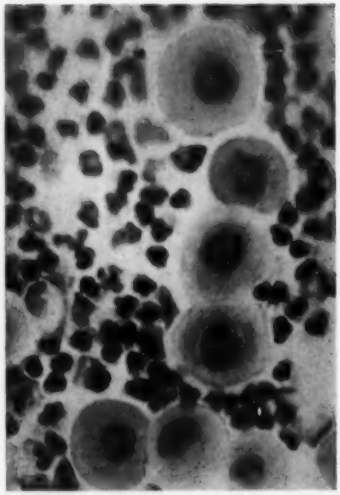

FIG. 4

Photomicrograph of vaginal smear from normal virgin guinea-pig at Stage IV of oestrus. The smear shows a decreasing number of rounded epithelial cells and numerous leucocytes. No lipoid is present in the epithelial cells. Stained Sudan III and Haematin. ×475.

FIG. 5

Photomicrograph of section of vaginal wall from normal virgin guinea-pig at Stage I of oestrus. The superficial epithelial cells contain coarse droplets of lipoid which appear black in the photomicrograph, and some of the cells are being shed into the lumen. These cells show appearances identical with those of the vaginal smear at this stage. Compare with Fig. 1. Stained Sudan III and Haematin. ×150.

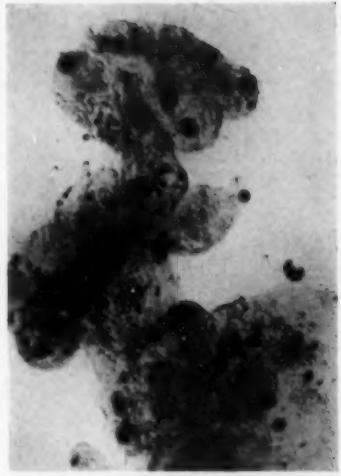

FIG. 6

Photomicrograph of vaginal smear from double ovariectomized guinea-pig treated with oestrogen. The cells are typical of the first stage of oestrus and contain coarse droplets of lipoid which appear black in the photomicrograph. Compare with Fig. 1. Stained Sudan III and Haematin. ×475.

THE LOWER UTERINE SEGMENT

BY

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SINCE the publication of Shaw and Nirula (1951) new material has been obtained and old material re-examined in the light of more recent observations.

METHODS

The same method, low power photography of stained sections, with or without light filters, was used. The sections which varied in thickness from 3 to 6μ were stained with Harris's Haematoxylin and Eosin and by a modified Mallory and Picric Acid stain. Rather more use was made of naked eye inspection.

DEFINITIONS

The following are the important terms for consideration:

The *isthmus uteri* of Aschoff was described as a specialized portion of uterus lying between corpus and cervix uteri. The *anatomical internal os* is at the junction of corporeal and isthmic mucosa. The *histological internal os* lies 6 to 10 mm. below this and is in the plane of transition from isthmic to cervical mucosa. The term *obstetrical internal os* describes the junction of ovum chamber and cervical canal. In the non-pregnant uterus, it coincides in position with the anatomical os but this relationship is lost in pregnancy.

As at present described, the *physiological retraction ring* is the lower edge of the relatively thick active *upper segment* of the uterus in labour. The *lower segment* is the thinner, less active part of the uterus *in labour*, which lies between the physiological retraction ring and the obstetrical internal os. At present, reference to a lower segment *before labour* is undesirable.

THE STRUCTURE OF THE NON-PREGNANT UTERUS

Musculature

Musculature appears in the wall of the uterus during the 4th month of intra-uterine life. By the 10th month well-defined layers develop from the primitive mesenchyme. In relation to the epithelial lining a layer of condensed interlacing muscle fibres differentiates. This is separated from an external layer, predominantly of longitudinal fibres, by a zone of blood-vessels. No clear picture of cervical structure in the prenatal period has been obtained. Sometime later the distinction between layers is partially lost and they seem to blend, becoming obvious again only in response to pregnancy or pathological conditions (Fig. 1). Nevertheless, the non-microscopic method reveals their general arrangement into zones. It is convenient to continue to refer to these zones as layers for they remain potential layers and are redeveloped in pregnancy.

The fibres of the external layer are predominantly longitudinal. Fibres pass in other directions but the resultant muscular force remains longitudinal. The layer occupies the outer quarter of the myometrium. It sweeps up and over the fundus and is continuous below with the external longitudinal layer of the vagina. Muscle fibres split off from the main muscle to form a layer, the external or extrinsic muscle of the cervix, beneath the mucosa of the portio vaginalis cervicis (Hughesdon, 1952). A fossa marks the anterior firm attachment of peritoneum to uterus (Shaw and Nirula, 1951). This provides an index to movement of the longitudinal layer in pregnancy.

The condensed interlacing layer is developed in close relation to the basal layer of the endometrium and the mucosa of the isthmus uteri. It occupies the inner one-half to two-thirds of the myometrium, being bounded externally by an ill-defined zone containing blood-vessels and immature muscle fibres in a matrix of collagen. Traced down the isthmic segment the condensed interlacing layer suddenly thins and continues as a thin extension beneath the endocervical

mucous membrane. It will be convenient to refer to this as the internal cervical muscle. The thinning of the condensed interlacing layer shows, on section, as a cone formation, the apex of which usually lies about two-thirds of the way down the isthmic segment. As a concomitant, the intermediate zone, traced down the isthmus, thickens to form the bulk of the cervix below the level of the cone. At the level of the anatomical os, that is a short distance above the cone, the uterine wall is kinked. In this way is formed the obstetric internal os and the normal angle of anteflexion. The development of the internal cervical muscle varies from specimen to specimen. Commonly, fibres curve round at the level of the external os to join fibres of the external cervical muscle arching over the vaginal fornix.

It will be noted that, above the cone, the middle layer is thin and the internal layer is thick whereas, below the cone, the middle layer is thick and the internal layer thin.

Mucosa

The relation of muscle cone to anatomical and histological ora has been mentioned. As Frankl (1933) asserted, these mucous membrane rings can, in most specimens, be distinguished visually. The anatomical os is easier to define for endometrium is thicker and softer than isthmic mucosa. The histological os is not represented by the upper limit of the arbor vitae but by a shallow furrow just above this point. Check microscopy has confirmed this. It is uncommon, however, to find a uterus in which the isthmus is not overlapped by either the projection of endometrium from above or the cervical mucosa from below. Further observations were made on pregnant uteri.

The Changes of Pregnancy

(Some of these may be followed in Fig. 2)

The First 5 Months

During these months certain changes take place in the organization of uterine musculature. The division into layers becomes more obvious and the fibres themselves undergo hypertrophy and hyperplasia. The condensed interlacing fibres exhibit this property rather more than the external longitudinal fibres and the part of the uterus above the cones is more affected than the cervix. This results in two notable points which may be observed in the 10-week uterus. The isthmic musculature hypertrophies, resulting in elongation of its segment. As will be shown, the anatomical os ring bears a very close relation to the underlying muscle and some elongation of the isthmic mucosa occurs also. Danforth (1947) found that the histological os ring was rather higher than in the non-pregnant uterus. The other point of note is that the differential growth of the muscle layers results in an upward movement of the external longitudinal layer. The anterior firm attachment of peritoneum and its marker, the fossa, follow the movements of this layer and are drawn upwards (Shaw and Nirula, 1951). Even at this early stage, differential movement of the layers is observed.

The hypertrophy of the muscle of the isthmic segment is most striking before the conceptus has filled the available space in the body of the uterus (Danforth, 1947). When this point is reached, in the third month, the isthmic musculature unfolds and is "taken up" into the ovum chamber—a process analogous to the taking up of the cervix at term. The kink in the uterine wall unrolls and passes down to the level of the apices of the muscle cones. The obstetrical os is then formed by the apices of the cones. Thinning of the uterine wall, due to size of contents, does not occur until the isthmic reserve has been used up, a process incomplete before the fifth month.

An operation specimen of a 5-months pregnancy shows interesting features in these respects (Fig. 3). The ovum chamber is a regular spheroid, the lowest part of its walls being the unfolded isthmic segment and the obstetrical os being formed by the apices of the muscle cones. In this specimen, the histological os lies in the same plane. A centimetre above the obstetrical os a few fibres, separated from the inner aspect of the muscle mass, become attached to the mucosa of the anatomical os and through it to membranes. This represents a firm attachment of mucosa to internal fibres comparable to that of peritoneum to external fibres. It determines a fixed relationship between anatomical os ring and muscle cone. Between the firm attachment and the histological os ring is the hypertrophied isthmic mucosa. Finally, rotation of the muscle cones from almost vertical to almost horizontal—an

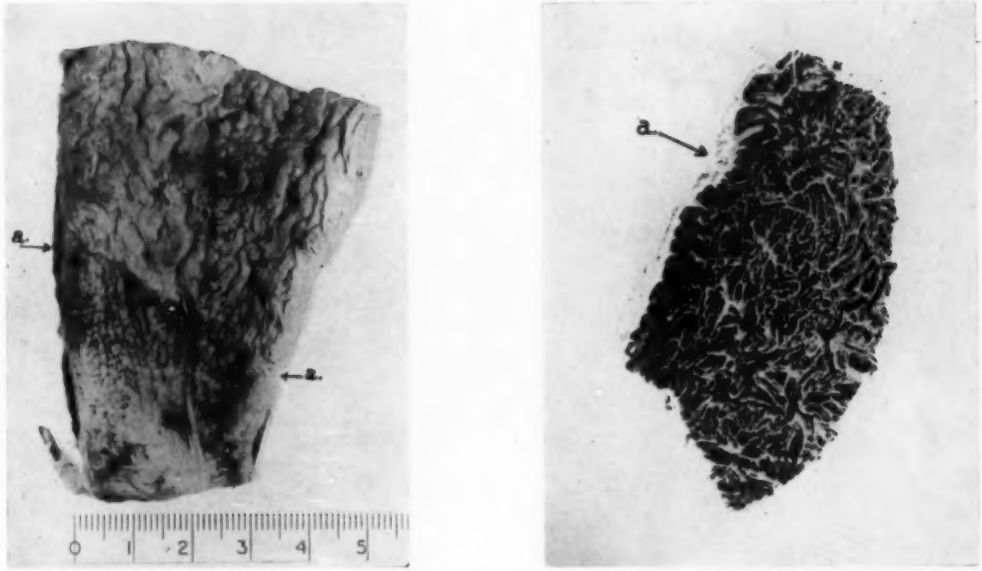
FIG. 1

Oblique section of a uterus and ovary removed at post-mortem from a girl, aet. 7 years, with congenital heart disease. Venous congestion has rendered the middle vascular zone prominent and thus differentiated the external and internal layers. ×5.

FIG. 3

A 5-month pregnant uterus removed by total hysterectomy. The lower pole of the spheroid is formed by the unfolded isthmic segment. The cones form the obstetrical os and the internal cervical muscle is seen streaming down from their outer aspects. The external cervical muscle in this and the other specimens illustrated, has been distorted by post-vital retraction. ×2.

C.P.W.S.



(1) (2)

FIG. 4

(1) Part of a uterus removed before term by Caesarean hysterectomy. The membranes have been stripped from the left half of the specimen. The anatomical os ring is clearly seen and the difference in texture between corporeal and isthmic segments will be appreciated. $\times 1\frac{1}{2}$. (2) A section from the same specimen showing the structure peculiar to the anatomical os and, again, the difference in structure above and below it. $\times 4$.

FIG. 5

A section of anterior uterine wall from a 36-week pregnant uterus removed at post-mortem. A thick corporeal wall gives place to a thinned isthmic segment below which is a thick cervix. The isthmic segment is laminated and the isthmic portion of the internal cervical muscle is thicker than the cervical portion. The middle layer has almost disappeared from the isthmic segment but remains thick in the cervix. It appears that the isthmic portion of the internal cervical muscle has thickened at the expense of the middle layer. Just above the obstetrical os, decidua is seen overhanging the honeycomb-like cervical mucosa. Muscle fibres split off from the inner side of the main mass are seen in the upper part of the section. $\times 1\frac{1}{2}$.

(1)

(2)

FIG. 6

(1) A uterus ruptured in labour and removed by subtotal hysterectomy. The cone-shaped retraction ring has the lower segment attached to its outer margin. The lower segment shows marked layering. (2) Section of lower segment from the same specimen, showing the internal, middle and external layers with cleavage planes between. ×4.

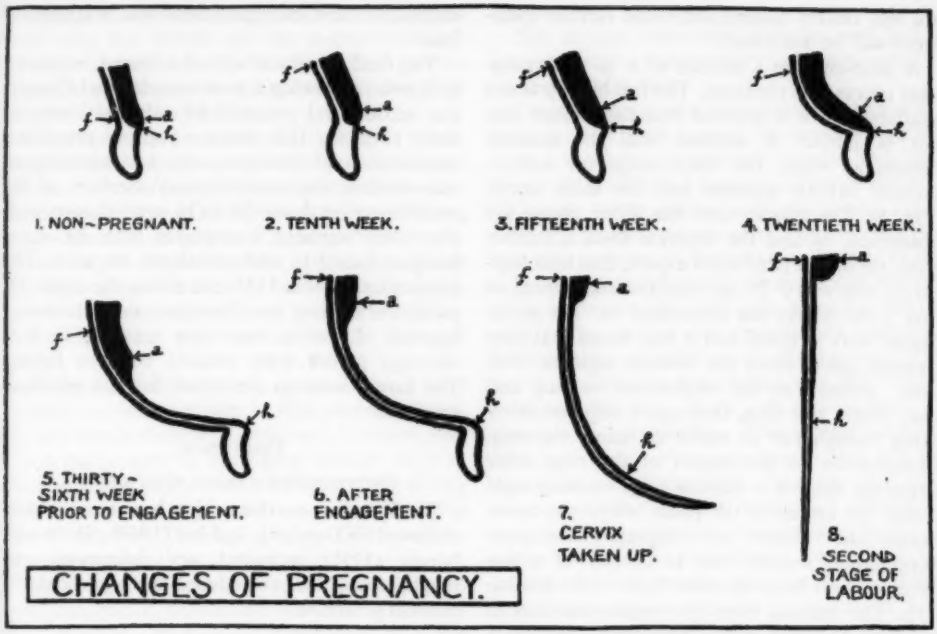


FIG. 2

Schematic representation of some of the changes of pregnancy. The lower part of the anterior uterine wall is shown in section. The curve of the birth canal is not represented, nor are the differences in the thickness of the cervical muscles at various stages. f = anterior fossa. a = anatomical os. h = histological os.

1. *Non-pregnant.* The muscle cone is $\frac{2}{3}$rds of the way down the isthmus uteri. Above it, there is a thick internal layer and a thin middle layer: below it a thin internal layer and a thick middle layer. 2. *Tenth week.* Relations are similar. The isthmus uteri has hypertrophied. 3. *Fifteenth week.* The isthmus has unfolded. 4. *Twentieth week.* The muscle cone has rotated from near vertical to near horizontal and the internal cervical muscle is continuous with its outer aspect. 5. *Thirty-sixth week, prior to engagement.* The muscle cone has been drawn up. Below it there is a thin internal layer and a thin middle layer. The diameter of the muscle ring is less than that of the foetal head. 6. *After engagement.* The diameter of the ring is more than that of the foetal head which has passed through it. 7. *Cervix taken up.* The cervix has been effaced from above and thinned. 8. *Second stage of labour.* The cervix is fully dilated, the lower segment is further thinned and the cone and upper segment have thickened.

inherent part of unfolding—has altered the relations of the internal cervical muscle. It appears to be continuous not with the apex of the cone but with its outer margin. In this specimen direct microscopy of the histological os was possible. The site of the anatomical os in this specimen, and of the histological os in later specimens, was easily determined by naked eye inspection. Fig. 4 shows the correlation between microscopic and macroscopic views of the anatomical os ring later in pregnancy. Use was also made of the characteristic difference in the way in which membranes stripped from the isthmic and corporeal segments and the muscular attachment so revealed (Fig. 5).

This then is the state of affairs at the 20th week. At this time *conversion* from spheroid to cylindroid occurs and uterine enlargement is by stretching and elongation of fibres rather than their hypertrophy and hyperplasia (Gillespie, 1950).

The Second 5 Months

The changes of the second half of pregnancy

are less clearly understood. Two further specimens will be described.

A post-mortem specimen of a 36-week pregnant uterus was obtained. The full history is not available but it is believed that the woman was not in labour. It showed well the mucous membrane rings, the thick corporeal wall, a thinned isthmic segment and the thick cervix (Fig. 5). The muscle cone was 4 cm. above the obstetrical os and the anterior fossa a further 2 cm. up on the peritoneal aspect. The histological os ring was 0·25 cm. and the anatomical os ring 5 cm. above the obstetrical os. The membranes were stripped and it was found that they stripped easily from the isthmic segment, that they "pulled" at the anatomical os ring and that, above this ring, they again stripped fairly easily though not so easily as below the ring. Examination of the region of the ring, after stripping, showed a definite ridge running right round the uterus at the place where the membranes had "pulled" on stripping. Histological examination showed this to consist of a few fibres split off from the inner layer of the muscularis. The mucosa over this region was lost in stripping but, nearer the histological os, was a characteristic decidua which actually overhung the cervical mucosa. A gland in this overhanging portion shows distinct gravid changes. Below this was high columnar epithelium.

Examination of the musculature of the cervix and isthmic segment was revealing. The cervix consisted of a relatively inert, mainly collagenous centre, enclosed by internal and external cervical muscles. The isthmic segment appeared thinned and laminated. The muscle cone was higher up the uterine wall than in earlier specimens and the internal cervical muscle was considerably longer, comprising an isthmic and a cervical portion. The layers of the thinned isthmic segment were, from within outwards, isthmic mucosa, isthmic portion of internal cervical muscle, thin middle layer and external layer. It is not difficult to picture the development of this arrangement from that of the 5-month uterus. Differential movement of the internal and middle layers has taken place, the muscle cone has risen and the thin middle layer lately related to it is now related to the isthmic portion of the internal cervical muscle drawn up after the cone. Details of the mechanism and its implications will be discussed later.

The final specimen was of a uterus, ruptured in labour, following a previous classical Caesarean section and removed by subtotal hysterectomy (Fig. 6). The anterior rupture precluded examination of the fossa, etc. and histological examination was unsatisfactory. Section of the retraction ring showed it to be cone-shaped with the lower segment continuous with its outer margins lateral to and just above the apex. The anatomical os was 1·25 cm. above the apex. Of particular interest was the structure of the lower segment. Layering was very marked, in fact cleavage planes were present between layers. The layers were as described for the previous specimen.

Discussion

(*incorporating clinical observations*)

The literature on this subject has recently been reviewed by Danforth and Ivy (1949); Shaw and Nirula (1951) indicated key references and Hughesdon (1952) considered more particularly cervical structure.

The Non-pregnant Uterus

The description of the non-pregnant uterus here given may be correlated with that of recent contributors. Thus the fibromuscular junction of Danforth (1947) corresponds to the apex of the muscular cone. The relations of the mucosal rings to this structure, as described by Danforth, have been confirmed. He did not, however, recognize a muscle pattern in the cervix. The methods of examination used did not lend themselves to this. In the non-pregnant uterus the upper cervical muscle of Hughesdon (1952) corresponds to the thick internal layer above the cone. He described the extrinsic or external muscle of the cervix and, also, the internal cervical muscle though he attached little importance to the latter.

Mechanisms in Pregnancy

The concept of re-arrangement of muscle bundles and differential movement of layers is more readily accepted after study of the loosening of collagen fibres in pregnancy. Hughesdon (1953) recognizes 3 components: the separation

of collagen fibres by fluid; the division of fibres into very fine fibrils and the re-absorption of fibres with replacement by fluid. The process affects the collagen matrix between, rather than within, the muscle bundles.

Mention must be made of response to stress. Hughesdon described a relative prominence of circular muscle around the obstetrical os after unfolding of the isthmus. He attributed this to rearrangement in response to centrifugal strain. Observations suggest that the application of this principle is more wide and that the normal response to stress throughout the uterus is rearrangement or organization in the lines of stress.

Differential movement in pregnancy is a vital process occurring slowly so that shearing forces do not divide the layers. In labour, however, and more particularly in obstructed labour, the process is more mechanical and less vital, taking place comparatively quickly so that shearing forces produce cleavage planes differentiating the layers.

Emphasis has been laid upon rearrangement and differential movement for these processes are observed throughout pregnancy and are essential to the formation of the lower uterine segment.

The First 5 Months

As a result of hyperplasia and hypertrophy, the isthmic segment elongates and then in unfolding yields before the growing conceptus. The palpation of the empty elongated isthmic segment, before unfolding, constitutes Hegar's sign. By this time, the mechanisms have produced more marked lamination of the uterine wall, relative upward movement of the external layer and a functional sphincter at the obstetrical os. Classical descriptions include an incomplete internal layer of circular fibres prominent around the openings of the Fallopian tubes and around the obstetrical os. This layer has not been defined as separate from the interlacing layer. It will be appreciated that the overall effect of contraction of a ring of interlacing fibres will be sphincteric. Disruption of this functional sphincter by high amputation or deep laceration of the cervix may be associated with habitual abortion at this stage.

The Second 5 Months

The changes occurring in the second half of pregnancy have received less attention owing to paucity of material.

The description of a 9-month uterus here given is considered to be typical. The muscle cone has risen, the internal cervical muscle has been drawn up after it and has responded to stress by becoming better defined and elongated; differential movement has occurred, resulting in a thin isthmic segment. Danforth and Ivy (1949) suggest that the fibromuscular junction remains as the obstetrical os until term. Shaw and Nirula (1951) suggest that the cone is not drawn up until the time of "lightening". Hughesdon (1952) has shown that, in the normal case, the "upper cervical muscle" forms the obstetrical os throughout pregnancy. The upper cervical muscle is a leash of mature muscle fibre running across the top of the cervix. In early pregnancy it corresponds with the condensed interlacing layer and cone. In late pregnancy, however, it corresponds with the isthmic portion of the internal cervical muscle which has elongated and been reinforced in response to stress. In such cases the muscle cone is found to be drawn up and not at the obstetrical os.

A study of specimens, atlases (reviewed Barbour, 1889), personal observations and those of others, in pregnancy, labour and at operation (e.g. Davis, 1949; Nixon, 1950) has led to the following conclusions: (1) that differential movement occurs and that the muscle ring, represented on section by the cone, is slowly drawn up beginning soon after the 20th week, (2) that the slow drawing up, implying slow dilatation of the muscle ring, persists until labour commences and (3) that the very slowness of the process allows vital reorganization and adjustment of relations between muscle, decidua and chorion. Thus shearing forces do not produce cleavage planes and vessels are not ruptured.

It will be appreciated that, with slow dilatation of the muscle ring, a point will be reached when the foetal head can just pass it and, in doing so, sinks deeper into the pelvis: the act of engagement. Foetal attitude may also depend in part upon the muscle ring. The head, previously above the brim, incompletely flexed and mobile, in the act of engagement becomes completely

flexed and less mobile. It is not difficult to imagine chance movement of an incompletely flexed head resulting in the coincidence of its smallest circumference with the dilating muscle ring. As the smallest circumference is sub-occipitobregmatic, engagement with a fully flexed vertex presentation is effected.

In some cases, the muscle ring may not dilate fully until term. The result is a functional high head, floating free above the brim, seeming, as indeed it is, to be held up by the soft tissues. Late engagement in multiparae has a similar basis.

As the ring dilates, the conceptus is normally supported by the reinforced isthmic portion of the internal cervical muscle and the collagen framework of the cervix. Muscle tonus is the most important factor, collagen becoming more important when this is relaxed. In some cases of abortion occurring after the 20th week Hughesdon (1952) has demonstrated a relative deficiency of mature muscle fibres around the obstetrical os. He interprets this as due to precocious movement of the upper cervical muscle. It is suggested that, in such cases, the immediate cause is a failed mechanism: namely, the response to stress of the internal cervical muscle. Failure to reinforce this muscle as the muscle ring dilates would result in a relative deficiency of mature muscle fibres around the obstetrical os. It is further suggested that the failed mechanism is due to disruption of the cervical tissue below the muscle ring. This condition exists in most multiparae but, because dilatation of the muscle ring occurs late, is seldom followed by abortion. If the ring dilates early, the unsupported membranes bulge into the cervical canal and abortion is induced.

The Origin of the Lower Uterine Segment

The conclusion reached by Shaw and Nirula (1951), and supported by these observations, is that the physiological retraction ring has its origin in the muscle cone ring. The latter is drawn up and with it the elongated isthmic mucosa governed by the fixed relation of anatomical os to muscle cone. The layers of the lower segment are thus isthmic mucous membrane, isthmic portion of internal cervical muscle, a thin intermediate layer, external longitudinal layer and peritoneum. The lower limit of the lower segment is the obstetrical os. Its relation to cervical mucosa depends upon the variations in effacement and dilatation of the cervix.

As the lower segment forms, differential movement continues. As the muscle cone ring is drawn further up, the difference in level between it and the anterior fossa is reduced. This is readily confirmed at Caesarean section before labour.

Taking Up and Allied Processes

The following description is based on that of Hughesdon (1952). It has been stressed that loosening of the cervical collagen does not affect the connective tissue within the muscle bundles. Through their organized collagenous frameworks, the internal and external cervical muscles transmit "the pull of the lower and upper segments to the cervix. The tangential relation of these (muscles) . . . to the rest of the cervical tissue is important. Their advancement or retardation relative to one another is associated with variations in the anatomical pattern during taking up and dilatation of the cervix." Relevant factors would appear to be the difference in forces exerted on the two muscles and the difference in resistance at the site of application of those forces. Resistance may be due to muscular spasm or tissue consistency. On this basis, all the variations in anatomical pattern may be explained. Hughesdon has drawn particular attention to "taking down" of the cervix, a process in which the external os dilates and the cervical canal is effaced from below upwards. This has not been infrequently observed and has enabled the prediction of a long first stage to be made.

The Lower Uterine Segment in Labour

The layers of the lower uterine segment continue to undergo differential movement. This is a more marked and more mechanical process than in pregnancy and takes place comparatively quickly. The shearing forces resulting produce cleavage planes and differentiate layers. The process is even more marked in obstructed labour and its results are obvious in museum specimens of ruptured uterus. The anterior fossa and muscle cone are further approximated and may be found at the same level. As would be expected in obstructed labour, the fossa may be found below the retraction ring.

The lower uterine segment is capable of contraction and retraction though, for anatomical reasons, it is less strongly active than the upper segment. It is believed that, in normal labour, the lower segment exhibits these properties but that they are overshadowed and perhaps overcome by the power of the upper segment. In the first stage of labour the lower segment thins and may undergo longitudinal shortening due to circumferential dilatation. Danforth and Ivy (1949) believe that, under normal circumstances, longitudinal elongation occurs only during the second stage of labour. As labour advances, the lower segment becomes thinner and the upper segment becomes thicker. Their junction, the physiological ring, becomes more distinct and advances cephalad. Should labour be obstructed, progressive thinning and elongation of the lower segment may result in its rupture.

After the second stage of labour the empty lower uterine segment collapses beneath the weight of the upper segment and placenta. It is then distended by the placenta passing through the birth canal after which it again collapses beneath the contracted upper segment. By the third day of the puerperium the process of involution has resolved the difference in thickness between corporeal and isthmic segment (Barbour 1889). The lower uterine segment is effaced and ceases to exist as an entity.

Summary

Further observations on uterine musculature have been made. In the non-pregnant, pregnant and labouring uterus, a thick condensed internal muscle layer ends inferiorly in a cone-shape representing a muscle ring. A thin internal condensed layer continuous with the cone-shape is found beneath the isthmic and endocervical mucosae. The mechanisms of re-arrangement and differential movement permit the change in relations of the internal muscle layer which have been traced throughout pregnancy and labour. In labour the cone-shape is identified with the physiological retraction ring and thus the tissue below it with the lower uterine segment.

I am indebted to Mr. Wilfred Shaw for helpful criticism, specimens and photographs, and to Mr. D. B. Fraser, Mr. A. O. Gray and Mr. J. Howkins for specimens. At St. Bartholomew's Hospital the sections were prepared by Mr. Bert Cambridge, other photographs by the Department of Medical Photography and help with the literature was given by Mr. John L. Thornton, Medical College Librarian.

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A CASE OF QUINTUPLET PREGNANCY

BY

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ONLY 74 cases of quintuplet pregnancy have so far been reported in the literature in the past two centuries. It is believed that the case described here is the first one in the British Isles.

Lawrence and Pauli (1951) record a total of 71 cases of authentic quintuplet pregnancy. Two further cases are described by Nichols (1950) and another case is described by Kachin and Naimagon (1952). Only 2 sets of quintuplets have survived, the Dionne quintuplets of Canada and the Diligenti quintuplets of the Argentine, described by Beruti in 1944.

CASE REPORT

A woman of 35 years was admitted to the Kent and Canterbury Hospital on the 8th January, 1953. Her last menstrual period had started on the 12th June, 1952; she was thus 30 weeks pregnant by her own dates. She had had 4 normal deliveries before, giving birth to infants which weighed between 6 pounds (2·72 Kg.) and 9½ pounds (4·31 Kg.). During her previous pregnancies she had been perfectly well but in this pregnancy she had not felt well enough to carry out her household duties. Her legs had been swollen for 2 months and she had felt no movements for 2 days prior to admission. She complained of headaches but no visual disturbances.

On examination she was pale and had marked oedema of the legs and abdomen. There was hydramnios and the girth of the abdomen was 44½ inches (113 cm.). Her blood-pressure was 150/100. No foetal parts could be felt nor could a foetal heart be heard.

A catheter specimen of urine taken on the following day revealed a slight trace of albumen but no bacterial growth. Her haemoglobin was 66 per cent and an X-ray of the abdomen showed the presence of quintuplets (Fig. 1). One foetus was presenting by the breech and 4 by the vertex.

The patient was treated by complete rest in a darkened room and large doses of sedatives and iron were administered. Her blood-pressure fell to 120/80 by the evening of the day following admission. The oedema diminished, revealing numerous varicose veins, the albumen disappeared from the urine and her fluid output was adequate. The foetal hearts were never heard.

At 8.30 p.m. on the 14th January, 1953, labour commenced spontaneously and by 10.15 p.m. the cervix was fully dilated. A bulging bag of membranes was ruptured artificially; the liquor was brownish in colour. Twenty minutes later the first stillborn macerated foetus was delivered spontaneously. Within the next half an hour 4 others had been born, the last one necessitating a breech extraction.

Intravenous ergometrine, 0·5 mg. (1/120 gr.), was given. The placenta separated but was caught in the cervix. A general anaesthetic of nitrous oxide, oxygen and ether was given and the placenta removed manually. The total loss was 10 ounces (284 ml.). Both the tone of the uterus and the mother's general condition were excellent after delivery. Involution occurred satisfactorily and the patient was discharged on the 29th January, 1953. Her haemoglobin on the 19th January was 76 per cent and the urine contained no albumen.

The infants, all male, weighed between 2 pounds 8 ounces (1·13 Kg.) and 3 pounds (1·36 Kg.), with a total weight of 13 pounds 12 ounces (5·78 Kg.). The placenta was large, weighing 2 pounds (0·907 Kg.) and had 5 cords arising from it (Fig. 2).

COMMENT

Clinically this case presented with severe toxaemia of pregnancy which responded well to

FIG. 1
Lateral view of abdomen showing 5 foetal skulls.

FIG. 2
Placenta with 5 cords arising from it.

rest. There was a large amount of liquor but in spite of this the uterine contents were expelled without difficulty within an hour. There was no postpartum haemorrhage and the placenta had only to be assisted through the cervix. Involution was good and there was no sign of toxaemia after delivery.

My thanks are due to Mr. J. K. Baker for permission to record this case and to Dr. F. L. Ingram for the X-ray photograph.

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INTRAVENOUS PITOCIN BY THE DRIP METHOD IN THE INDUCTION OF LABOUR

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IN 1908 Blair-Bell first introduced the use of posterior pituitary extract in obstetrics. The indication was to stimulate uterine contractions, particularly in cases of postpartum haemorrhage; but its use was also suggested prior to the birth of the baby, in cases of primary or secondary uterine inertia.

However, the indications were widened considerably by the unwary, and many disasters followed. The dangers of the indiscriminate use of the drug during this period could be summarized as follows:

1. Potency of the drug varied from batch to batch as biologic standardization was difficult.

2. There was a variable amount of vasopressor substance in the original "pituitrin", a factor of considerable importance in dealing with hypertensive patients.

3. Individual susceptibility to the drug varied immensely, as shall be discussed in detail later. The same dose might, in one patient, cause no increase in uterine tone or contractions and, in another, a state of prolonged uterine tetany.

4. Unrecognized cases of cephalo-pelvic disproportion, or indeed other forms of obstructed labour, were misdiagnosed as simple delay due to "poor pains" and often treated by huge doses (by present-day standards) of pituitrin. This led, on occasions, to uterine spasm, contraction rings, foetal asphyxia and, not infrequently, uterine rupture.

By the third decade of this century most teachers were condemning out of hand the use of pituitary extract in labour prior to the birth of the baby. However, as a method of medical induction of labour, the use of small repeated doses of this drug, following the time-honoured oil, bath, and enema, has slowly been adopted in most centres.

Today, pitocin, a purified extract, allegedly containing virtually no pressor factor and now well-standardized, has replaced the older pituitrin, and has become almost standard practice, given at ½ hourly intervals in doses of 2 or 3 minims to a total of 1 ml.

Many writers have stressed the dangers even in this dosage, particularly the unpredictability of uterine response and the ever present worry of a uterine spasm.

In discussing the management of cases of uterine inertia, however, one has found but occasional reference in the literature to the use of pitocin, and always a timorous approach, with great stress on the potential dangers.

An inertia of undoubted hypotonic type, with complete relaxation between contractions, a well-flexed, engaged head with no suggestions of cephalo-pelvic disproportion, and a taken-up, well applied cervix, were essential prerequisites. It was then suggested that small doses of pitocin might be tried, under careful watch, to gauge the response, always ready immediately to damp down contractions with chloroform, other anaesthetic agents or antispasmodics.

The idea of administering posterior pituitary extract by the continuous intravenous route was first put forward by Theobald *et al.* (1948). They used as diluent 500 ml. of physiological glucose-saline solution, and quoted a series of cases with encouraging results, both in the induction of labour and in selected cases of uterine inertia.

Recently, American writers have further advanced the idea of pitocin given intravenously by the "drip" method. Hellman (1949) advanced its use in functional uterine dystocia, quoting a small series of successful cases. His impression was that the controllability, when such dilute solutions are given by intravenous "drip", justified its cautious use to combat uterine inertia in unobstructed labour.

Then, in 1952, came two reports (Mauzy and Donnelly, 1952; Baptisti, 1952) of intravenous pitocin drips in the induction of labour, with particular reference to the interruption of pregnancy complicated by severe pre-eclampsia, in the patient with the firm uneffaced cervix—the so-called "unripe" cervix.

It has been the teaching in many British schools of obstetrics that the only safe method of interrupting a pregnancy before the 34th week, when urgent indications exist, is by Caesarean section. Furthermore, it is well-known that, where the cervix is long, firm and uneffaced, induction by any means is difficult. Medical inductions are unsatisfactory and rarely succeed. Surgical rupture of the membranes—either by high or low rupture—when the cervix is "unripe" may be followed by a lag period of several days before labour is established, with the ever-present danger of an intra-uterine infection, in spite of the prophylactic use of antibiotics.

Where the cervix is favourable, surgical induction by membrane puncture is still our most potent method and, alternatively, Caesarean section still has a definite place where there is a sense of urgency, particularly in rapidly deteriorating toxaemic patients.

Following these overseas reports, we decided to try the efficacy of an intravenous pitocin drip, if necessary repeated daily, in converting the unripe, closed and uneffaced cervix of a toxaemic primigravid patient with a 32-weeks pregnancy, to a cervix that was "safe" for surgical induction of labour, in other words, the soft effaced cervix with the presenting part well applied, and the external os readily dilatable to admit at least 2 fingers.

Our results in our first few cases were sufficiently encouraging to persuade us to carry out an investigation on the action of pitocin drips. We have widened our indications considerably, and have gained most valuable personal experience by staying with the patient for many hours during the running through of the intravenous solution. We have now completed 55 cases of the use of intravenous pitocin, either as a form of medical induction, as a method of induction combined with membrane puncture, or as a preliminary to membrane puncture.

With experience we have gained confidence in its use, have learnt something of the varying response of the uterine muscle in different patients, and have begun to clarify our ideas on dosage.

Our next step has been to assess the effect on cases of uterine inertia, and again the results have been encouraging.

We feel the essential feature of the intravenous drip method of pitocin administration is that the effect is continuous and *sustained*. So often small doses of intramuscular pitocin have only a fleeting action, and yet the dangers of increased dosage, or more frequent injections, are such that one cannot persist with the administration by that route. How often are the routine injections of the standard medical induction stopped because of the temporary presence of painful contractions, and yet labour is not established?

We have learnt in this present series that the pitocin drip can be carried on throughout the entire labour and, indeed, during the third stage. Rapid separation of the placenta can be achieved with minimal blood loss.

Our present impression is that, in certain cases of inertia, some degree of control over the uterine forces can be achieved. In one case a pitocin drip was continued throughout labour until the presenting part was almost "crowned" and the patient was ready for delivery. At this stage, the drip was stopped. The uterus remained inert for the next 45 minutes. The drip was recommenced, within 5 minutes regular contractions were re-established and the patient had an easy spontaneous delivery.

Procedure and Technique in the Induction of Labour

Intravenous pitocin is such a powerful drug, and its use fraught with such danger, that we feel the procedure should be carried out only in a fully equipped obstetrical hospital. It demands the whole attention of a member of the medical staff during the entire procedure, and the patient must never be left unattended at any stage.

When interruption of pregnancy is decided upon, a careful vaginal examination is made, noting the state of the cervix, the degree of effacement and of dilatation, and its application to the presenting part. The presentation and degree of engagement should be noted, and any possible cephalo-pelvic disproportion, or other causes of dystocia, eliminated. Where rupture of the membranes would appear safe and the most suitable procedure, it should be performed, to be followed by the pitocin drip. If surgical induction is contra-indicated, the drip alone is used, with the hope of either establishing labour or "ripening" an otherwise unfavourable cervix. This process may take several days to achieve and it may be necessary to repeat the drip daily with graduated doses of pitocin.

We prefer to administer pitocin in the daytime for a period of 6 to 8 hours. If labour does not supervene, the patient is returned from the delivery room to her ward, and a good night's sleep ensured.

Daily examinations of the state of the cervix and the station of the presenting part are noted prior to each successive drip, and so progress is defined. After the initial vaginal examination, adequate information can usually be obtained by repeated rectal examinations.

Though labour may not be established by this means alone, it is hoped that there is sufficient alteration in the state of the cervix to render surgical induction reasonably certain of success.

Dosage

We quote the dosage in minims for ease of measurement, using the standard preparation of 10 units per ml.

We began by using 1 minim of pitocin in 500 ml. of 5 per cent glucose, and were somewhat surprised by the definite effect noted even in this extreme dilution. As we have gained confidence we have increased our initial dose to 2 minims and finally 5 minims. However, we would recommend 2 minims as an initial dose, until the nursing and medical staff are fully conversant with the procedure, and with the varying degrees of uterine response. Where it has been necessary to repeat the drip, we increase the dose daily by 2½ minims. As diluent we recommend 500 ml. of 5 per cent glucose; saline being contra-indicated because of the large proportion of toxaemic patients.

We use a 2-bottle technique. An intravenous drip of 5 per cent glucose is set up by venepuncture. A second bottle containing 5 minims of pitocin is then set up to form a Y-attachment, the needle of the pitocin-containing bottle piercing the rubber tubing of the first drip apparatus as close as possible to the patient. Thus if a switch is made back to glucose alone there is virtually no lag.

The pitocin bottle is then cautiously switched over at a rate of 6 to 8 drops a minute. Usually within 5 minutes, although in some cases the period may be longer, a perceptible hardening of the uterus occurs. The contractions of the uterus at the onset are not painful to the patient, but they can be felt by the observer, and the duration, frequency, and intensity recorded. *Complete relaxation of the uterine muscle must occur between contractions, and the contractions must not be prolonged.* It is our aim to achieve contractions lasting approximately 45 seconds every 3 to 4 minutes, with complete relaxation between. It may take 2 hours or more to reach this ideal. Furthermore, the uterine rhythm may be extremely variable at first. We feel that, after the drip has been running for 30 minutes at a certain rate, with no untoward reaction, the rhythm should be stabilized for that dosage of pitocin. We can then safely increase the rate by several drops. Should relaxation not be complete, or individual contractions last longer than 60 seconds as an upper limit, the drip must immediately be slowed, and if necessary, a switch back made temporarily to the glucose bottle.

Initially the foetal heart should be listened to every 5 minutes. Any suspicion of foetal embarrassment requires immediate cessation of the

pitocin, and, later, its cautious resumption. Once a regular rhythm is established the foetal heart rate should be recorded ½-hourly.

No drip may be started unless an ampoule of amyl nitrite is on the patient's locker by her bedside. If, at any stage, a uterine spasm should occur, this drug may be administered immediately by inhalation. Furthermore, it is probably advisable to have facilities available for immediate anaesthesia should the spasm be other than temporary. In this series no case of spasm has occurred that has not been relieved by switching immediately to the pitocin-free bottle.

Theoretically, the rate can be increased even to a drop a second, but in practice we have never found it advantageous nor necessary to increase the rate higher than 30 drops a minute. A very rough working rule would be to increase the rate by 4 drops every ½ hour, where necessary.

Should the contractions become sufficiently intense and painful to suggest that labour is definitely established, especially if rectal examination confirms this, our routine is to switch to the glucose for 1 hour. If, at the end of this time, there has been a significant diminution in the quality of the pains we have cautiously reintroduced the pitocin; if not, we have been certain of the success of an induction, and the administration discontinued.

Recently, however, with increasing experience and confidence in the method, we have carried on longer with the pitocin, provided that the relaxation between contractions was completely adequate and the foetal heart satisfactory. Several recent cases have been carried on through the third stage. We have had no reason to regret this procedure, and though our series is, as yet, too small to draw conclusions, we feel the possibilities are considerable.

The majority of our cases have been in toxaemic patients. During this procedure, the maternal condition must be carefully watched. A rapid deterioration in the toxaemic condition may indicate Caesarean section at any stage as the quickest method of terminating the pregnancy. The maternal pulse and blood-pressure are charted hourly together with the routine 4-hourly urine testing.

Several cases of uterine inertia have been treated by intravenous pitocin drip but are not included in this series. However, when a woman is in labour, the dangers in its use are much greater than when used as a form of induction of labour. The inertia must be hypotonic in character, with complete uterine relaxation, malpresentation or disproportion must be excluded, and there must be no evidence of prior foetal embarrassment. A further word of warning is added that uterine vulnerability to rupture by oxytocics increases markedly with parity.

Results

Number of Cases treated	55
Indications for Induction of Labour:	
Toxaemia of pregnancy	33
Eclampsia	2
Rh iso-immunization	6
Diabetes complicating pregnancy	5
Premature rupture of the membranes	4
Postmaturity	3
Accidental antepartum haemorrhage	1
Congestive heart failure complicating pregnancy	1
Total	55
Number of primigravidae	22
Number of multigravidae	33
Maternal mortality	Nil
Stillbirths (macerated)	2
Neonatal deaths	5
Total foetal wastage	7
Cases in which labour successfully established	52
Cases considered as failures	3
	55

Presentation

In this series there were 3 cases of breech presentation and one case of anencephaly, presenting as such. The remainder were cephalic presentations.

Also in the series were 2 sets of twins and 1 patient who had had a previous Caesarean section. All the latter were safely delivered following pitocin drip.

Method Adopted

We have stated in detail, earlier in this paper, our procedure of selecting cases for induction, into 3 categories:

1. Treated by pitocin drip alone, if necessary repeated daily.

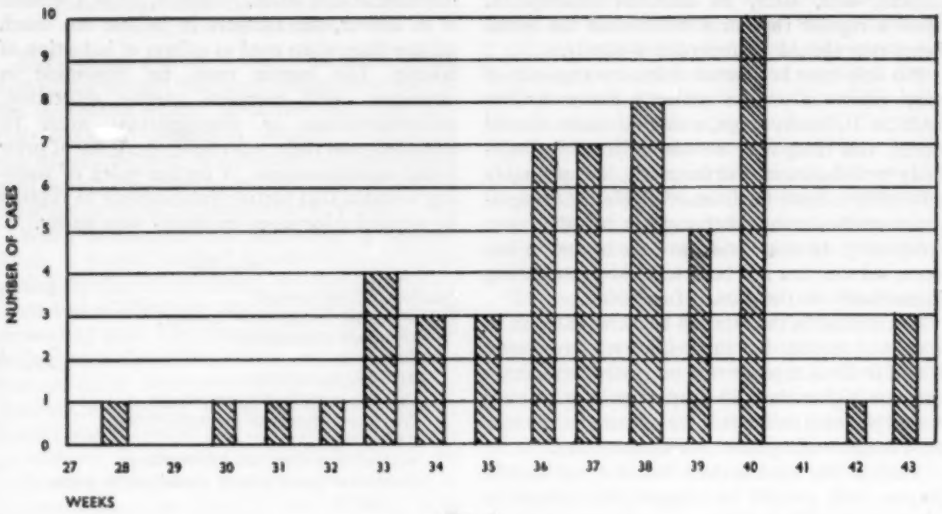

FIG. 1
Duration of Pregnancy.

2. Preliminary membrane puncture followed by pitocin drip.

3. Pitocin drip, if necessary on successive days, as a preliminary to membrane puncture, and then followed by a further pitocin drip.

On this careful selection will depend the success of each group; thus, if preliminary membrane puncture was decided upon, we anticipated that, together with the first pitocin drip, labour would be established, as conditions were already "ripe"; and this usually proved to be the case. If a pitocin drip alone was decided upon, it will be seen that it was either successful on the first occasion, or was part of the "preparation" for surgical induction.

In no case following this procedure did the subsequent post-membrane-puncture drip fail to establish labour.

(A) *Pitocin Drip as a preliminary to artificial rupture of the membranes*

There was a total of 17 successful cases. In 7 a drip on one day only sufficed to prepare the previously "unripe" cervix; 2 required 2 days, and 8 drips in graduated dosages on 3 successive days. All were established in labour during the pitocin drip following the artificial rupture, and were successfully delivered. This group is mainly made up of cases of severe pre-eclamptic toxaemia in primigravidae before the 36th week of pregnancy.

A typical case history is quoted:

Mrs. L.H., aged 27 years, a primigravida, was admitted on 4th February as an emergency at 35-weeks gestation, with a moderately severe pre-eclamptic toxaemia. Her blood-pressure was 170/90, there was slight ankle oedema and a catheter specimen of urine showed ¼th albumen. Over the next 2 weeks her condition remained substantially the same, under routine toxaemic treatment of bed-rest, adequate sedation, salt-free diet etc. All renal function tests were satisfactory. The urine continued to show small amounts of albumen and the blood-pressure remained around 160/100. On 17th February, at 37-weeks gestation, induction of labour was decided upon. The presentation was a vertex, R.O.A. position, the head was well engaged. Vaginal examination showed the head to be well engaged—the cervix 1 inch long, firm, and admitted the tip of the finger. A pitocin drip containing 5 minims in 500 ml. of glucose was commenced at 8 drops a minute. No contractions were perceptible until the rate was increased to 16 drops, when they commenced. At 24 drops a minute, a rhythm of regular contractions was achieved, but ceased on completion of the drip.

The patient was returned to her ward. The following day vaginal examination showed a cervix of ½-¾ inch long, soft, and admitted one finger. A pitocin drip containing 10 minims was commenced, and at a rate of 12 drops a minute regular contractions commenced. The drip was slowly increased to 24 drops and run through at that rate. Again contractions ceased on completion of the drip and the patient was returned to her ward for a good night's sleep.

Next day, 19th February, vaginal examination revealed the cervix much softer, less than ½ inch thick, and with the presenting part well applied. It was readily dilatable to 2 fingers. Drew Smythe rupture of the hind waters was performed and 22 ounces withdrawn. The forewaters were also ruptured. A third pitocin drip was started, containing 15 minims in 500 ml. of glucose. Labour was definitely established 3 hours after commencing the drip and the patient was delivered by low forceps of a healthy child that same evening. She had an uneventful puerperium and on discharge from hospital her blood-pressure was 140/90 and her urine was albumen-free.

(B) *Artificial Rupture of the membranes followed by Pitocin Drip*

There was a total of 26 cases. All but 4 were successful inductions on the first pitocin drip. In 4, the drip was repeated on the second day and the patient safely delivered.

(C) *Treatment by Pitocin Drip alone*

There was a total of 12 cases in this series, 8 of whom were successful on the first drip and one required a drip on 2 successive days. The remaining 3 cases in this group are considered as the only failures of the whole series, and will be considered in detail.

Failures

1. A primigravida, aged 22 years, admitted at 37 weeks with pre-eclamptic toxaemia. After 8 days in hospital, induction was considered to be advisable. Vaginal examination disclosed a long uneffaced cervix with a closed os; the head was engaged. Pitocin drips were given on successive days in doses of 5 minims, 7½ minims, and 10 minims. Daily examination showed some softening and taking up of the cervix but surgical induction was not deemed advisable. Her toxaemic condition had improved, and it was decided to wait for several days. A week later a further drip containing 15 minims was commenced. However, the patient appeared to have developed an acute sensitivity to pitocin. All cautious attempts at introducing the drug led to uterine spasm, and no rhythm could be established. The drip was withdrawn. The following day her toxaemic condition showing further deterioration, a lower segment Caesarean section was performed, and a living child obtained.

2. A multipara, aged 30 years, with a history of 5 previous vaginal deliveries of full-time infants, was admitted as an emergency with a history of ruptured membranes for 4 days and allegedly 2 weeks postmature. X-ray following admission showed an adequate pelvis, but the presentation was a brow with the head engaged. The foetus appeared of full maturity with no apparent abnormality.

The following day the presenting part appeared to be entering the pelvic brim. A repeat X-ray showed a vertex presentation, L.O.P. position. Two days later conditions appeared identical on abdominal palpation, and a pitocin drip was commenced. Rhythmic contractions were established, but the foetal heart became unsteady and meconium appeared in the liquor. The head was high and obviously deflexed. A further X-ray showed that the presentation had reverted to a brow. Immediate lower segment Caesarean section was performed and a living child obtained.

3. A primigravida, aged 20 years, was admitted as an emergency with a slowly deteriorating pre-eclamptic toxaemia at 38 weeks. The presentation was an unengaged breech with flexed legs. The pelvis was roomy. A previous attempt at version under anaesthesia had been unsuccessful. Induction because of her toxaemic condition was considered advisable. Vaginal examination disclosed a very long hard uneffaced cervix, tucked up in the hollow of the sacrum. The presenting part was not engaged.

Three pitocin drips on successive days achieved no significant alteration in the state of the cervix, and indeed on no occasion were satisfactory rhythmic contractions achieved. Lower segment Caesarean section was performed and a living child obtained.

Stillbirths

There were 2 stillbirths in the series, both being cases of foetal death *in utero* occurring in cases of eclampsia admitted as emergencies. In both cases foetal death was diagnosed prior to any attempt to induce labour.

Neonatal Deaths

There were 5 in the series, one anencephalic monster (admitted as an emergency with premature rupture of the membranes), 2 cases of severe erythroblastosis, and 2 premature babies of severely toxaemic mothers. One was of barely 28-weeks gestation, and weighed 1 pound 12 ounces, and one of 32 weeks which weighed 2 pounds 9 ounces.

Summary and Conclusions

1. A method of administration of pitocin by the intravenous route in the induction of labour is presented.

2. There were no maternal accidents, and no apparent ill-effects on the baby that could be attributed to the pitocin.

3. The dangers are stressed, and a method of rigid supervision has been evolved.

4. It is most likely to be effective where conditions are favourable, and where other methods of induction usually succeed. However, it is our real impression that its action under these circumstances is more sure and more controllable than intramuscular pitocin.

5. We feel that its main advantage is in cases of the "unfavourable" cervix several weeks from term. It appears to "prepare" the patient for surgical induction with a reasonable chance of success, and so reduce the rate of Caesarean section in the interruption of pregnancy in these cases.

6. The possibilities of the use of intravenous pitocin, in cases of uterine inertia and prolonged labour, appear considerable, but will be discussed in a future paper.

Acknowledgments

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RESPONSE OF THE "PHYSIOLOGICAL ANAEMIA" OF PREGNANCY TO IRON THERAPY

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INCREASED blood-volume has been accepted, for a number of years, as the primary cause of the "physiological anaemia" of pregnancy. Because the anaemia of pregnant women has been considered physiological, lower normal limits than in non-pregnant women have been accepted for the haemoglobin level. Whitby and Britton (1950) suggest 10 g. haemoglobin per 100 ml. (68 per cent Haldane) as the lower normal limit in pregnancy. Roscoe and Donaldson (1946) attempted to define normal limits according to age and parity, and suggested that the expected level in the later months of pregnancy should be from 83 per cent at 20 years to 76 per cent at 35 years.

The part played by iron deficiency in the "physiological anaemia" of pregnancy, and the role of iron in its treatment have, however, remained controversial. Young *et al.* (1946) Laurell (1947), Cartwright and Wintrobe (1949), Lundström (1950) and Ventura and Klopper (1951), of the more recent authors maintain that there is a tendency towards iron deficiency during pregnancy. Wolff and Limarzi (1945) and Rath and Finch (1949) consider it unnecessary to give iron to pregnant women unless there is evidence of frank pathological anaemia. Adair, Dieckmann and Grant (1936) and Evans (1943) even state that iron given in pregnancy will not maintain the normal haemoglobin level. The purpose of this paper is to show that most pregnant women would appear to benefit from iron therapy.

For several years it has been the practice at King's College Hospital to perform routine haemoglobin estimations at about the 32nd week of pregnancy, and to treat with iron those women with haemoglobin levels (Haldane) of less than 80 per cent (12·2 g. per 100 ml.). Women thus treated were seen subsequently at intervals until shortly before term. A review of the results suggested that, in a majority of cases, the treated women showed a striking response to iron, even though many of them had had initial haemoglobin levels between 70 and 80 per cent, that is, within the range of "physiological anaemia". The rise in haemoglobin level seemed to be more than could be explained by the natural remission of the "physiological anaemia" towards term as various workers have suggested, and we formed the impression that our treated patients reached term with much higher haemoglobin levels than those not so treated. As a result the following investigation was planned, and arranged so that the points enumerated below could be examined:

(1) The effects of iron therapy on a group of pregnant women compared with a similar untreated group.

(2) The variation within the groups to see if there was in fact any remission of the anaemia towards term in untreated cases.

(3) The effect of iron therapy on pregnant women with a haemoglobin level of over 80 per cent.

COLLECTION OF MATERIAL

Pregnant women were seen at about the 32nd week of pregnancy and, if put on iron therapy,

at fortnightly intervals thereafter until term. If not treated, they were seen again at 36 weeks. All patients admitted to hospital for confinement had blood taken before delivery. Iron was administered in the form of 2 uncoated ferrous sulphate tablets (BP) taken thrice daily.

At the commencement of the investigation pregnant women with haemoglobin levels of less than 80 per cent were treated and those over 80 per cent left untreated. Later this arrangement was reversed except that we excluded every patient with an obvious hypochromic anaemia.

Blood for each haemoglobin estimation was obtained by venepuncture, so that the packed cell volume, mean corpuscular haemoglobin concentration and serum iron could be estimated, and variations, due to the use of venous and capillary bloods on different occasions, avoided.

The haemoglobin was estimated by Haldane's method (100 per cent=14·8 g. per 100 ml.), using the same standard throughout and limiting the number of observers to 5. The anticoagulant used was that of Heller and Paul (1934) and the serum iron was estimated by the method used by Davidson and Jennison (1952).

Women were selected so that the groups would be as nearly comparable statistically as possible. During a period of 6 months 221 women who were believed to be 32 weeks pregnant were seen. After delivery, only 174 were shown by back calculation to have been between 30 and 34 weeks pregnant at their first visit, and to have continued their pregnancies to term. Of these 174, we excluded a further 89 cases for one or more of the following reasons:

(1) Irregular attendance as out-patients.

(2) Absence of full-time results in the case of district deliveries.

(3) An initial haemoglobin level of less than 70 per cent or more than 88 per cent.

The remaining 85 patients were divided into 4 groups as follows:

Group A. (26 cases) Untreated. Initial haemoglobin 80-88 per cent.

Group B. (19 cases) Treated. Initial haemoglobin 80-88 per cent.

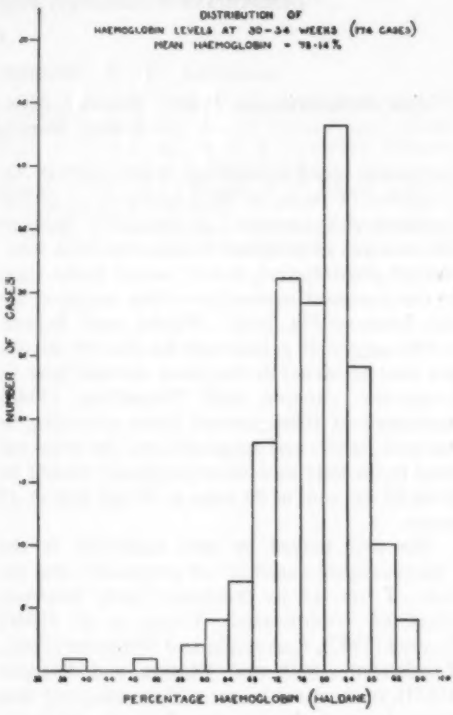
Group C. (20 cases) Untreated. Initial haemoglobin 70-78 per cent.

Group D. (20 cases) Treated. Initial haemoglobin 70-78 per cent.

Results

The distribution of the initial haemoglobin levels of the 174 cases is shown in Fig. 1. The observed mean agrees with that of other authors Magee and Milligan (1951), Benstead and Theobald (1952), Ventura and Klopper (1951), and Young *et al.* (1946).

FIGURE 1


DISTRIBUTION OF
HAEMOGLOBIN LEVELS AT 30-34 WEEKS (174 CASES)
MEAN HAEMOGLOBIN = 78·14 %
NUMBER OF CASES
PERCENTAGE HAEMOGLOBIN (HALDANE)

Figs. 2 and 3 show the results obtained in the 4 groups. The haemoglobin levels and packed cell volumes show a marked rise in the groups which have been treated with iron (B and D) as compared with the corresponding untreated groups (A and C). There is no appreciable change in the mean corpuscular haemoglobin concentration in groups A, B, and C, but a slight increase in group D.

Tables I-IV show the results in more detail. The values for 34-38 weeks have been omitted

for simplicity. Statistical analysis of the results by Fisher's "t" test gave the following results:

(1) The range of haemoglobin values at term in the treated groups (B and D) is within the normal range for non-pregnant women. The corresponding values in the untreated groups (A and C) show a much wider scatter.

(2) At term the treated groups (B and D) show significant differences in haemoglobin levels and packed cell volumes from the corresponding untreated groups (A and C).

(3) The treated groups (B and D) show a significant rise in haemoglobin levels and packed cell volumes from their initial levels. The slight rise in the untreated groups (A and C) is not significant except in the case of the packed cell volumes in group A; this is, however, much less than that in the corresponding treated group B.

(4) There is no significant difference between the mean corpuscular haemoglobin concentrations in treated and untreated groups at term but, within group D itself, there is a significant rise.

(5) The initial serum iron levels in each group are not significantly different. The rise in serum iron in group D (treated) compared with group C (untreated) is significant, although there is not a corresponding difference between A and B.

FIGURE 2

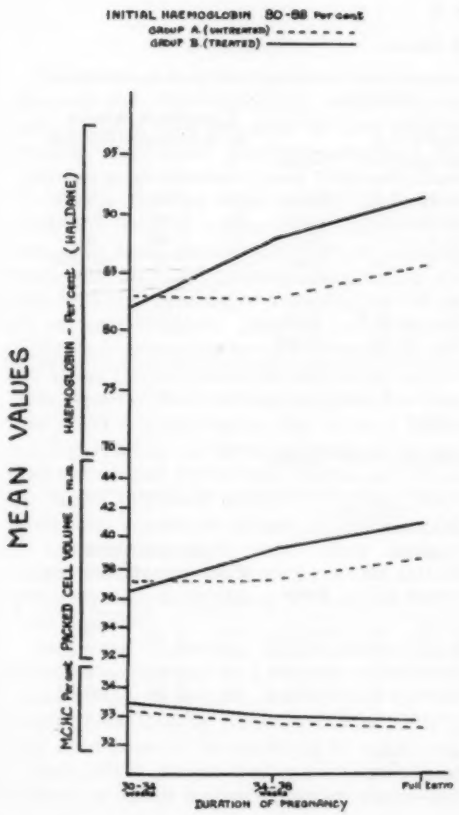


FIGURE 3

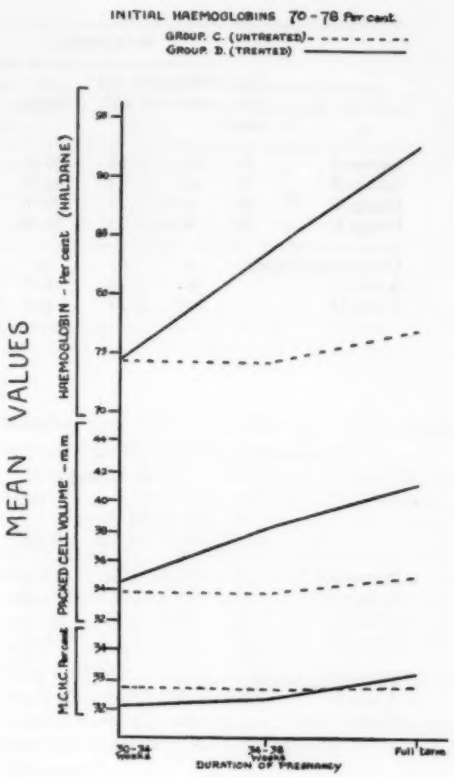


TABLE I

Haemoglobin Levels

	No. of cases	30-34 weeks: Mean Hb. per cent and S.D.	30-34 weeks: Range	Full-time: Mean Hb. per cent and S.D.	Full-time: Range	Comparison between 30-34 weeks and full-time: n	t	p
Group A ..	26	83 ±2·60	80-88	85·7±8·06	66-102	50	1·65	0·1
Group B ..	19	82 ±1·94	80-88	91·5±6·40	80-100	36	6·36	<0·001
Group C ..	20	74·4±2·37	70-78	76·9±5·93	70-90	38	1·75	0·1
Group D ..	20	74·6±2·35	70-78	92·4±6·00	80-102	38	12·30	<0·001

Comparing Groups	n	t	p	n	t	p
A and B	43	1·45	0·2	43	2·65	0·02
C and D	38	0·27	0·8	38	8·20	<0·001

TABLE II

Packed Cell Volumes

	No. of cases	30-34 weeks: Mean P.C.V. (mm.) and S.D.	30-34 weeks: Range	Full-time: Mean P.C.V. (mm.) and S.D.	Full-time: Range	Comparison between 30-34 weeks and full-time: n	t	p
Group A ..	26	37·2±1·48	35-41	38·81±3·82	29-48	50	2·01	0·05
Group B ..	19	36·5±1·98	32-40	41·16±2·91	35-47	36	3·05	0·001
Group C ..	20	33·8±1·32	31-37	34·9 ±2·77	31-43	38	1·60	0·1
Group D ..	20	34·6±1·67	31-38	41·2 ±2·67	35-46	38	9·37	<0·001

Comparing Groups	n	t	p	n	t	p
A and B	43	1·38	0·2	43	2·25	0·02
C and D	38	1·69	0·1	38	7·35	<0·001

TABLE III

Mean Corpuscular Haemoglobin Concentrations

	No. of cases	30-34 weeks: Mean M.C.H.C. per cent and S.D.	30-34 weeks: Range	Full-time: Mean M.C.H.C. per cent and S.D.	Full-time: Range	Comparison between 30-34 weeks and full-time: n	t	p
Group A ..	26	33·17±1·27	31·0-35·4	32·72±1·14	30·8-35·1	50	1·37	0·2
Group B ..	19	33·42±1·63	30·5-37·2	32·88±1·20	31·3-36·1	36	1·17	0·3
Group C ..	20	32·73±1·28	31·4-35·5	32·72±1·17	30·5-34·4	38	0·03	>0·9
Group D ..	20	32·12±1·64	29·8-36·4	33·18±1·35	30·2-35·0	38	2·24	<0·05

Comparing Groups	n	t	p	n	t	p
A and B	43	1·86	0·1	43	1·44	0·2
C and D	38	1·31	0·2	38	1·16	0·3

TABLE IV

Serum Iron

	No. of cases	30-34 weeks Mean Serum Iron (μg.) and S.D.	30-34 weeks Range	Full-time Mean Serum Iron (μg.) and S.D.	Full-time Range	Comparison between 30-34 weeks and full-time n	t	p
Group A ..	25	56·60±31·33	12-136	81·40±53·08	15-292	48	2·01	0·05
Group B ..	18	73·39±32·97	19-160	92·39±26·54	51-139	34	1·90	<0·1 >0·05
Group C ..	14	56·79±21·38	23-90	73·00±32·97	33-128	26	1·55	0·1
Group D ..	18	57·00±29·26	5-124	98·17±35·24	38-190	34	3·68	0·001

Comparing Groups	n	t	p	n	t	p
A and B	41	1·69	0·1	41	0·81	0·4
C and D	30	0·02	>0·9	30	2·06	0·05

DISCUSSION

Our results of iron therapy agree with those of Benstead and Theobald (1952), which showed that treatment with iron from the 16th week of pregnancy prevented the development of the "physiological anaemia", and treatment from the 24th to the 32nd week arrested its development and restored normal blood levels before term. For their survey these authors included cases with an initial haemoglobin level, at the 16th week of pregnancy, of over 11 g. per 100 ml. (74 per cent Haldane). They did not, however, divide their groups further. We have shown that our higher treated group (B) with initial haemoglobin levels of 80-88 per cent responded to iron. This result is confirmed by the work of Fisher and Biggs (1953). The mean and range of haemoglobin levels and packed cell volumes at term in the higher untreated group A is much wider. Some cases in group A showed a progressive fall in haemoglobin until term. These findings suggest that there is a tendency towards an iron deficiency state in pregnancy without necessarily overt anaemia.

Copp and Greenberg (1946) showed that increased absorption is a feature of iron deficiency states in general. Balfour and his colleagues (1942), using radioactive iron, showed iron absorption to be increased in pregnancy. Laurell (1947) showed that the iron-combining capacity is raised in iron deficiency states, and Ventura and Klopper (1951) showed a raised iron-combining capacity in pregnancy.

Increase in blood-volume was established by Dieckmann and Wegner (1934) and Thompson *et al.* (1938). These authors showed this increase to be 23-30 per cent, the plasma volume increasing by 40 per cent and the red cell volume by only 20 per cent. The failure of the red cell volume to rise in parallel with the increase in plasma volume is compatible with an iron deficiency state and this seems a probable explanation of the "physiological anaemia" of pregnancy. Lundström (1950) concluded that in pregnancy there is a tendency towards anaemia due to iron deficiency.

SUMMARY

A study has been made of the effects of iron therapy on pregnant women. The initial range of haemoglobin levels was 70-88 per cent (10·4-13·0 g.). The women were divided into similar treated and untreated groups above and below 80 per cent. Treatment resulted in both treated groups having haemoglobin levels at term within the normal non-pregnant range. The untreated groups showed no significant change. It is concluded that the "physiological anaemia" of pregnancy is due to insufficient haemoglobin and red cell formation to counteract the haemodilution caused by the hydraemia of pregnancy. The response to iron and all other evidence

available suggests that this is due to iron deficiency.

Acknowledgments

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OBSERVATIONS ON THE PULSE RATE DURING THE HUMAN MENSTRUAL CYCLE

BY

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BRIERRE DE BOISMONT (1842) noted that, in young girls, the pulse-rate was accelerated during "menstruation", and that the acceleration was sometimes accompanied by praecordial pain and dyspnoea.

Schmotkin (1912) made daily observations on the pulse-rates of 8 women, aged 18-25 years, during a period of 3 months but discovered no characteristic pattern. The observations were made between 2 p.m. and 3 p.m., without reference to rest or to the consumption of food, and the average rate obtained during the investigations exceeded 80 per minute.

Viville (1912) investigated the pulse-rates of 46 women of unstated ages during 47 menstrual cycles and found no characteristic pattern in them. The observations were made after 2 hours' rest in bed 3 to 4 hours after a midday dinner and, therefore, under approximately basal conditions. Unfortunately the original pulse records are not available and cannot be re-examined by modern statistical methods.

During the luteal phase of the menstrual cycle body temperature is elevated (Palmer, 1942) and, since it would be anomalous if a synchronous acceleration in pulse-rate did not occur, it was decided to re-investigate the relation of the pulse-rate to the human menstrual cycle.

METHODS

Radial pulse-rates were observed daily for 1 minute on 10 women, aged 18-25, healthy, unmarried, and free from the premenstrual syndrome (Greene and Dalton, 1953). The observations were made between 7 a.m. and 8 a.m. before rising from bed.

Table I presents the radial pulse-rates for each day of 22 menstrual cycles. The first 13 were consecutive cycles of 1 woman (Female No. 1), observed during a period of a year. The remainder were cycles of 9 different women observed during a period of 1 month each. Blank spaces denote days on which, due to intercurrent infection or other reason, records were not obtained, and dashes indicate days which were outside the limits of the cycles. In the case of Female No. 1 the cycles lasted from 25 to 29 days with an average bleeding phase of 4 days. In Females Nos. 2-10 they lasted from 26 to 29 days with an average bleeding phase of 5 days.

Fig. 1 presents a graph of the arithmetic means of the pulse-rates of Female No. 1 on each day of the menstrual cycles, and Fig. 2 presents corresponding data for Females Nos. 2-10.

Arithmetic means of the pulse-rates of any 2 groups of days during the menstrual cycle were regarded as "significantly" different when their actual difference exceeded twice the standard error of their difference (Hill, 1950).

Fig. 3 records the average daily basal oral temperature of Female No. 1, and Fig. 4 the average daily basal oral temperature of Females Nos. 2-10 during the period of the investigation. The daily records from which the graphs were constructed are not reproduced because no statistical examination of them is required.

The postovulatory rise in body temperature in the group of women (Fig. 4) was approximately 1 day later than in Female No. 1 (Fig. 3). Therefore the luteal phase of the group of women was regarded as beginning on the 15th day of the cycle, and the luteal phase of Female No. 1 was regarded as beginning on the 14th day of the cycle.

RESULTS

Female No. 1

Table I shows that the pulse-rate varied during the period of observation between a minimum of

TABLE I

Radial Pulse Rate on Each Day of 22 Menstrual Cycles

Day of Menstrual Cycle	Cycles of Female No. 1													Av. for each day of cycle	Cycles of Females Nos. 2-10									Av. for each day of cycle
	1	2	3	4	5	6	7	8	9	10	11	12	13		14	15	16	17	18	19	20	21	22	
1	60	62	63	63		64	58	65			68			64	62	70	65	56	60	54	68	72	67	63·8
2	63	60	58	60		62	60	64		58	61	61		61	62	65	65	58	60	52	68	72	74	64·0
3	65	61	61	56	67	64	60	59	64	63	70	59	69	63	70	74	63	58	60	48	68	72	60	63·8
4	61	64		65	60	63	62	60	64	65		61	68	63		70	65	58	60	52	62	70	56	61·6
5	64	60	70	65	60	62		65	61	58	65	69	68	64	65		72	60	60	54	60	64	61	62·0
6	63	57	70		59	58				65		61		62	55		62	63	60	48	68	76	60	61·5
7	58	62	56	63		60			64		65		68	62	62		68	60	64	46	63	66	64	61·6
8		65		57		60		60	64	67		63	60	62	58	76	66	60	60	48	58	64	64	61·4
9	55	63	63	63		66		65	64		67	61	65	63	55	76	64	51	62	49	74	74	65	63·3
10	60	60	62	64		63	60	64	72		65	69	65	64	60	74	68	54	62	47	70	66	80	64·6
11	58	61	60	69			58	70	72	65	59	68	68	64			75	60	58	52	64	72	72	64·7
12		63	57				60	70	69	63	72	60	58	63	60	72	58	75	60	57	60	68	72	64·7
13	58	63		64			58		64	66	65	68		63	53	75	52	60	60	54	60	72	72	62·0
14	58	65	65	54		61	60		74	70				63	55	76	63	65	60	52	64		56	61·5
15	59	70	70	64		63	62	58	66		60	60		63	57	72	66	60	64	49	66	74	72	64·0
16	60	53	63	66	60	63	62	63	60		68	68		62	60	70	64	71	60	50	64	72	62	64·0
17	63	60	77	68	64	66	62	66	69		65	63	64	64	60	74	70	65	62	58	64	72	68	66·0
18	65			64	62	63	60		65	60	64	62	65	63	60	74	68	68	60	52	64	76	62	65·0
19		59	60	62	66			64	65	70	68	63	69	64	62		72	68	60	54	60	74	68	64·8
20		60	64	68	68	64	68	72		71	68	68		67	65	78	68	78	62	55	56	76		67·2
21	58	63	61	64	64	59	68	61	67		73		72	64	56		70	58	60	54	60	66	72	62·0
22	63	65	59	72	62	64	61	63	60	60	65	69	68	64	60		68	58	62	49	58	74	72	62·6
23	66	60	60	66	64	64	63	64	60	65	71		70	65	60		67	58	58	52	60	76	72	63·0
24	66		60		64	60	68	74	60	61		61	68	64	62	76	70	65	60	54	66	64	68	64·3
25	68		63		64	62	68		68	71	65	63	71	66	60	74	72	65	60	55	66		60	64·0
26	61	60	55	—	58		59	66	62	68	68	67	69	63	60	70		54	74	54	58		62	61·7
27	60	72	65	—	62	60	65	—		62	71			65	—	76		65	78	56	68		80	70·5
28	61	—	—	—	64	—	—	—	—		—		—		—	70	70	68	—	57	53	—	54	61·8
29	—	—	—	—	—	—	—	—	—	74	—	—	—		—	—	—	—	—	52	—	—	—	

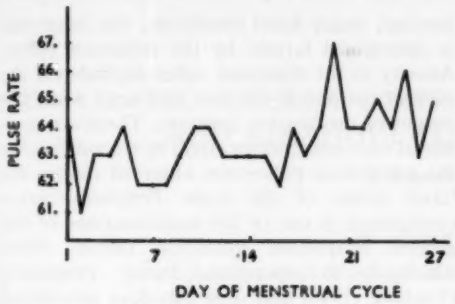

FIG. 1

Average pulse rate for each day of the menstrual cycles of Female No. 1.

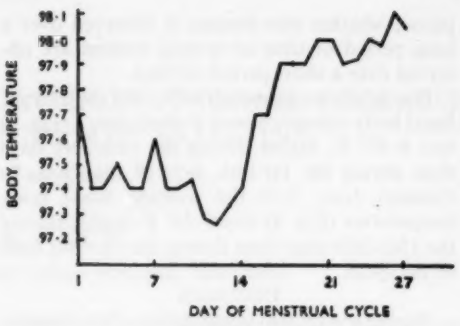

FIG. 3

Average oral temperature (Fahrenheit) for each day of the menstrual cycles of Female No. 1.

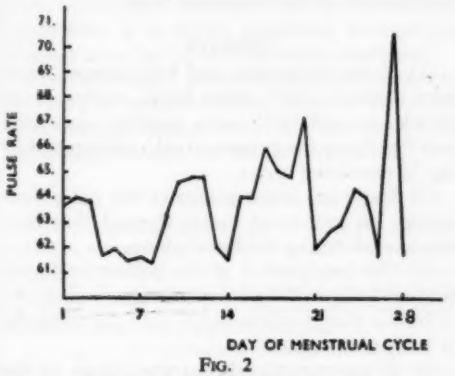

FIG. 2

Average pulse rate for each day of the menstrual cycles of Females Nos. 2-10.

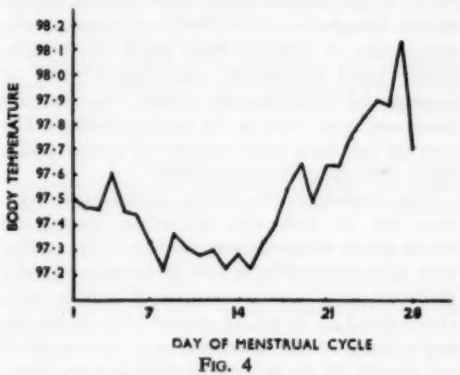

FIG. 4

Average body temperature (Fahrenheit) for each day of the menstrual cycle in Females No. 2-10.

53 per minute and a maximum of 77 per minute. The average was calculated to be 63·57 per minute.

The arithmetic means of the 1st-13th days and 14th-26th days are 62·5 and 64·0 respectively. Their actual difference is 1·5 and the standard error of their difference is 0·07. There is, therefore, overwhelming evidence that the pulse-rate of Female No. 1 is faster during the luteal phase than during the follicular phase of her menstrual cycles.

Females Nos. 2-10

Table I shows that the pulse-rate varied from a minimum of 46 per minute to a maximum of 80 per minute. The average was calculated to be 63·1 per minute. It also shows that the characteristic pulse-rate of 1 woman may be considerably different from that of another. For instance, the average rate for Female No. 7 was 52·2 per minute while that of Female No. 3 was 73·1 per minute.

The arithmetic means of the 1st-14th days and the 15th-28th days are 62·91 and 64·31 respectively. The actual difference between them is 1·4 and the standard error of their difference 0·135. They are, therefore, "significantly" different.

Therefore the average pulse-rate during the luteal phase of the menstrual cycle has been shown to be faster than during the follicular

phase, whether one woman is observed over a long period of time or several women are observed over a short period of time.

During the same menstrual cycles the average basal body temperature of Female No. 1 (Fig. 3) was 0·47° F. higher during the 14th-26th days than during the 1st-13th days of the cycle. In Females Nos. 2-10 the average basal body temperature (Fig. 4) was 0·26° F. higher during the 15th-28th days than during the 1st-14th days of the cycle.

Discussion

During the present investigations 265 observations on the pulse-rate of Female No. 1 and 209 observations on the pulse-rates of Females Nos. 2-10 were made. The averages were calculated to be 63·57 per minute and 63·8 per minute respectively. Graybel *et al.* (1944) investigated the pulse-rates of 1,000 fit men, aged 20-30 years, under basal conditions, and found them to average 63·8 per minute which, for practical purposes, is the same as the present findings. The average rate for a larger number of women under basal conditions is not available.

The demonstration by the present investigation that the pulse-rate accelerates during the luteal phase of the menstrual cycle is in conflict with the statement of Brierre de Boismont (1842) that the pulse-rate is accelerated during menstrual bleeding in young women. No doubt the explanation is that, a century ago, ignorance of the nature of the menstrual cycle created fear, and the fear was responsible for the cardiovascular manifestations he observed.

When body temperature rises the pulse-rate can be expected to increase by approximately 10 beats per minute per 1° F. (Wright, 1952), presumably due to direct action on the sino-auricular node. During the present investigation body temperature rose in the luteal phase of the menstrual cycle by 0·47° F. in Female No. 1 and by 0·26° F. in Females Nos. 2-10 and, therefore, the pulse-rates could have been expected to increase by 4·7 and 2·6 beats per minute respectively. In fact they rose by only 1·5 and 1·4 beats per minute. Apparently some restraint has been imposed on the heart rate during the luteal phase of the cycle preventing it from accelerating commensurately with the elevation in body temperature. The restraint will be of vagal origin because, under basal conditions, the heart-rate is determined largely by the depressor reflex. Activity in the depressor reflex depends on the state of peripheral vascular resistance when the output of the heart is constant. Therefore peripheral vaso-constriction could be responsible for the anomalous pulse-rates observed during the luteal phase of the cycle. Peripheral vaso-constriction is one of the manifestations of the general adaptation syndrome (Selye, 1950) which is in operation during pregnancy (Venning, 1946) and it is therefore postulated that corticoid activity is increased preparatory to pregnancy and is responsible for the failure of the heart-rate to accelerate commensurately with the elevation in body temperature during the luteal phase of the menstrual cycle.

Summary

(1) Radial pulse-rates and body temperatures were observed daily under basal conditions on 10 women aged 18-25 years, healthy, unmarried and free from the premenstrual syndrome, during 22 menstrual cycles.

(2) Statistical investigation of the pulse-rates during the menstrual cycles showed that they accelerated during the luteal phase.

(3) The acceleration of the pulse-rate during the luteal phase of the menstrual cycle was shown to be less than commensurate with the elevation in body temperature.

(4) It was postulated that the failure of the heart-rate to accelerate commensurately with the elevation in body temperature during the luteal phase of the menstrual cycle was attributable to increased corticoid activity.

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PERFORATED UTERUS COMPLICATED BY VAGINAL PROLAPSE AND STRANGULATION OF THE INTESTINE

A Report of Two Cases

BY

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IN the past 15 years 14 similar cases have been recorded in the literature, and of these only 6 cases are in the English literature.

Although perforation of the uterus is not a very uncommon accident during intra-uterine operations, it is rarely associated with serious damage to other intra-abdominal structures.

The following 2 cases are presented, however, not only on account of the rarity of the condition, but also because of certain uncommon and interesting features not hitherto recorded.

CASE REPORTS

CASE 1. A young primigravida, 23 years old, 3-months pregnant, was admitted on 18th August, 1949, as a case of incomplete abortion. About 12 hours previously she was treated by an untrained village midwife who had tried to terminate the pregnancy by manual and crude instrumental methods under septic conditions.

In view of the subsequent findings at operation her general condition on admission was remarkably good. She was not severely shocked, although she looked pale and anaemic. The haemoglobin was 40 per cent, the temperature 97° F., the pulse 84 per minute, the blood-pressure 106/72 mm.Hg.

The abdomen was soft and not distended except for some fulness over the suprapubic region; this disappeared on withdrawing 500 ml. of clear urine. There was no rigidity, but some tenderness was present over the hypogastrium and left iliac regions. Bowel sounds were absent. The vulva was lacerated and oedematous and a bluish cystic mass protruded at the vulva. When the vagina was examined with a speculum there was an escape of blood-stained fluid and bubbles of gas which were seen to be coming from a necrotic mass of strangulated gut filling the entire vagina.

Laparotomy was undertaken. The uterus was enlarged to about a 12-weeks pregnancy, and on its posterior wall was an oblique lacerated wound 4 cm. long extending to the left uterine vessels. Tightly gripped in this wound was a loop of ileum, which was completely gangrenous for several cm., both proximally and distally, the distal end being about 40 cm. from the ileocaecal valve. There was a transverse rent in the mesentery involving the vessels and this accounted for the massive gangrene of the ileum (Fig. 1). The affected part of the intestine with part of the mesentery was resected, 225 cm. in all, and the ends anastomosed. Supravaginal hysterectomy was performed instead of simple closure of the wound on account of the gross contamination and danger of gas-gangrene. The abdomen was closed without drainage.

Although neither blood-transfusion nor antibiotics were then available the post-operative period was uneventful. She made a rapid recovery and was discharged 2 weeks later.

CASE 2. A primipara, 26 years old, had vaginal hysterotomy on 29th December, 1950, for termination of a 4-months pregnancy on account of continuous bleeding.

During this operation the uterus was unwittingly perforated. A mass protruded into the uterine cavity which was then delivered into the vagina without the surgeon realizing what it was. At this stage the patient was severely shocked. Her pulse became imperceptible, the blood-pressure dropped from 108/74 to 60 mm.Hg systolic and the diastolic could not be recorded. Perforation of the uterus was diagnosed and the abdomen was immediately opened. The prolapsed intestine was reduced and the uterine wound sutured. However, continuous and uncontrollable bleeding made necessary an urgent hysterectomy. The affected part of the intestine was only with some difficulty recognized as almost the entire length of the pelvic colon. It was detached from its mesocolon except near the proximal 5 cm. and the distal 4 cm. In addition, the mesocolon was torn across, severing the sigmoid vessels. The superior haemorrhoidal had luckily escaped. About 4 cm. proximal to the recto-sigmoid junction there was a transverse tear through the bowel wall on its antero-medial aspect soiling the peritoneal cavity (Fig. 2). Through an oblique incision in the left iliac region the entire pelvic colon was exteriorized, the affected part was resected and the proximal-distal ends of the bowel were maintained in the wound with considerable difficulty.

After a stormy few days she made a good recovery, the wounds healing per primum. At the time she was discharged the terminal colostomy was functioning satisfactorily.

FIG. 2

The nature and extent of lesion of the pelvic colon and its mesocolon in Case 2.

DISCUSSION

It appears from the study of those cases recorded in the literature that in perforation of the uterus there may be a striking absence of the shock so evident in the perforation of other hollow viscera, such as the stomach or duodenum, a point which is worth bearing in mind. There is no doubt that this not unusual absence of the features of peripheral vascular failure accounts for the long intervals which occur in most of these cases before they are seen or treated, and also in the condition being overlooked.

It may be possible to treat some cases of perforated uterus conservatively in the absence of other complications. In the majority of the cases, especially if damage to extra-uterine structures is suspected, immediate surgical treatment is indicated. Simple closure of the wound of the uterus is the method of choice, particularly in young subjects. But under certain conditions it may be necessary to do hysterectomy as in the cases reported here.

In Case 1 hysterectomy was done on account of gross sepsis and danger of gas-gangrene, in the second case chiefly because of failure to control haemorrhage by all other methods.

The other unusual feature in both these cases is that the mesentery and the pelvic mesocolon were torn across. In Wolff's case (1948) and in the case reported by Glisson and Daniel (1951) the intestine was detached from the mesenteric attachment. But in neither of them was there an actual tear through the substance of the mesentery. This is a likely happening when excessive traction is applied by pulling on the prolapsed bowel during internal manoeuvres, as probably happened in these 2 cases. This is a serious complication, since, if the main arterial arcades are divided, widespread gangrene of the intestine occurs.

The most unusual feature in Case 2 is the involvement of the part of the colon. The rarity of such a complication is due mainly to the anatomical features of the large bowel. It is less mobile, shorter in length and wider in diameter than the freely mobile long loop of the ileum, and it is therefore less liable to herniate through a small opening. Prognosis in the case of large bowel strangulation is very much worse than where small intestine only is involved.

SUMMARY

Two cases of perforation of the uterus following induced abortion on primigravid patients are described. The first one was a case of criminal abortion with gross sepsis, prolapsed and strangulated ileum in the vagina associated with rupture of the mesentery.

In the second case the uterus was perforated during vaginal hysterotomy, and this was associated with herniation, strangulation, and partial rupture of the pelvic colon and rupture of the mesocolon.

Hysterectomy was performed in both cases for the reasons described. In Case 1 continuity of the intestine was restored by anastomosis, but in Case 2 only terminal colostomy was possible. Both cases recovered.

I am greatly indebted to Mr. M. R. Ewing of the Postgraduate Medical School of London for

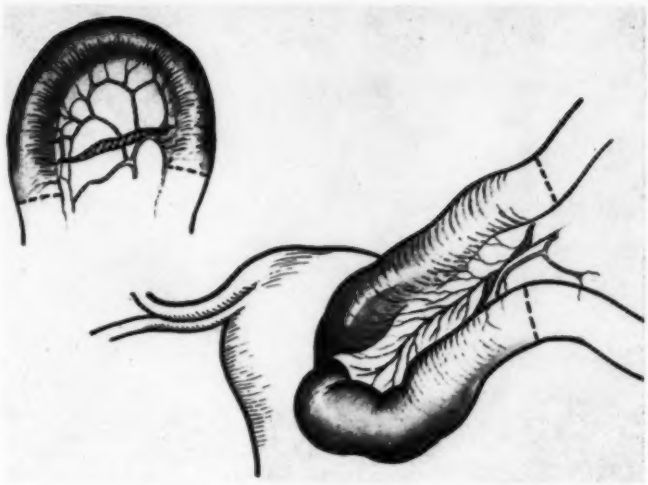

FIG. 1

The operative findings in Case 1. Strangulation of a loop of ileum through the perforated posterior wall of the uterus. The inset shows the rent in the mesentery across the vascular arcades.

M.C.

his advice on the preparation of this paper, and to Professor I. Aird for permission to have the diagrams made by the School artist, Miss Wilson, to whom I am thankful.

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FOETAL HEAD EXTRACTORS AND LOWER UTERINE SECTION

BY

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THIS instrument, which has been fully described elsewhere (Murless, 1948), consists of a single fenestrated blade with an exaggerated cephalic curve, which can fold back on its handle at a double hinge, thus enabling the blade to be introduced round the foetal head in lower segment Caesarean section (Fig. 1).

The instrument requires practice in handling before it can be introduced easily and quickly in certain cases where the head lies low in the pelvis. Surgeons, who by misfortune have met with such a case when trying out the instrument for the first time, have been disappointed and probably discouraged from further attempts, when a little practice with the average easy case would have enabled them to introduce the instrument successfully.

Weisman and Carrabba (1952) in this connexion state: "We advocate the use of the Murless blade routinely for residents and young obstetricians in the easy case in preparation for its real need in difficult cases."

CRITICISM OF THE HEAD EXTRACTOR

Certain criticisms of the instrument have come to the writer's notice and must be examined. They are listed below.

1. That such an instrument is unnecessary because the operator can achieve the same result by the use of his hand.

2. That the instrument is difficult to introduce with the head engaged in the pelvis and this is the only time it is really needed.

3. That the locking mechanism of the joint is inclined to stick and waste the operator's time.

4. That the blade is unnecessarily wide and strong for the work it has to do.

1. It has never been claimed that this instrument is an essential adjunct to the operation and no one will deny that the foetal head can always be delivered manually. The Extractor is in fact "a mechanical hand" a term aptly coined by Bonney (1953) and has obvious advantages over manual delivery.

The thin metal blade occupies far less room

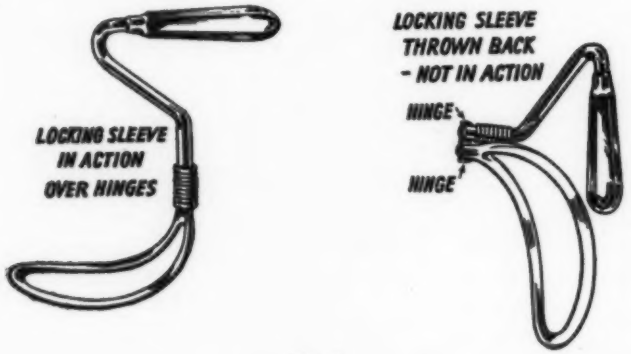

FIG. 1
The Murless head extractor

than the smallest human hand. The extremities of the uterine incision are clearly visible throughout the delivery. Thus uterine lacerations are avoided and a clumsy manipulation replaced by a neat surgical procedure.

2. Difficulty has been met with when attempts have been made to introduce the blade with the foetal head engaged in the pelvic cavity. It must be stressed that this instrument was not designed to deliver the deeply engaged head from the pelvis. Under these circumstances the head must be raised until the parietal eminence is level with the upper border of the symphysis pubis before the extractor blade can be introduced. The reason for this is well demonstrated in Fig. 3. It is possible this point was not sufficiently emphasized in the original publication.

In the vast majority of cases the head can be raised sufficiently by inserting 2 fingers into the uterine cavity. However, it is our experience that occasionally a deeply impacted case is met with where 2 fingers are inadequate to raise the head and it becomes necessary to insert 4 fingers and most of the hand to get the head up. Under these circumstances it seems a waste of time to replace the hand with the extractor before delivery, for any damage has already been done and it is our practice to scoop the head out manually. On this point I cannot entirely agree with Weisman and Carrabba (1952), who write of the extractor: "It is of inestimable value in difficult deliveries of the head when manual efforts at delivery of the head have failed."

In our last 100 sections myself and colleagues have encountered only 2 cases where the head could not be raised sufficiently with 2 fingers for the extractor to be introduced. Probably such cases rarely come to the table for section for when the head is so low vaginal delivery is usually feasible.

The head extractor is also useful when dealing with the abnormally high and mobile head, which is not always easy to bring out through a low uterine incision by standard methods. Such a case is easily dealt with by fundal pressure, intravenous ergot and the guiding action of the extractor blade.

3. Difficulty in working the sliding sleeve at operation has been noted by several surgeons. This was to a great extent due to the sleeve fitting too tightly on some of the earlier instruments, with the result that it was inclined to jam unless lubricated before each operation. Also, it must be remembered that as the sleeve covers two joints it is essential to straighten the shaft fully before it can slide into the locking position, a point sometimes overlooked when the apparatus is first used.

Any difficulty with this sleeve has been overcome by Weisman and Carrabba who have modified the instrument, incorporating an automatic locking sleeve which is described later.

4. It has been pointed out by Barnes (1953) that the blade could with advantage be made slightly narrower and of thinner metal making it easier to introduce. This is true as the stress on the blade should at no time be great and a lighter and thinner design with a slightly narrower blade should have sufficient strength. It must be remembered, however, that if the blade is made unduly thin, damage to the foetus or posterior wall of the uterus might become a possibility.

Advantages Claimed

The original claims made for the head extractor have not to my knowledge been seriously challenged and still hold good in the light of added experience. It may be permissible to re-state these.

1. The lifting action of the extractor holds the operation area in full view until the head has been delivered. Both ends of the uterine wound can be carefully watched throughout the manœuvre and at the same time haemorrhage from this area is reduced to a minimum.

2. Uncontrolled tearing of the uterus cannot occur if the head is delivered slowly.

3. The head can be lifted out in any position without tiresome manipulations.

4. No injury to a baby from use of the instrument has yet been reported. Compression injury would seem impossible with the use of a single blade. In over 300 operations we have encountered no case of foetal injury which could be blamed on the extractor.

5. The operation is easier, neater and quicker when the head extractor is used.

The Weisman-Carrabba Modifications

In 1952 Weisman and Carrabba of New York after working with the original extractor evolved

a modified instrument (Fig. 2). Although the apparatus is essentially similar it differs from the original in several important features.

1. The fenestrated blade is slightly narrower and of a lighter pattern. The widest part of the blade measures 5·3 cm. against 5·5 cm. in the Murless extractor.

2. The shaft bends on a single joint which is placed 5 cm. from the blade. In the original model the lower of the two joints is only 2·5 cm. from the blade. This extra 2·5 cm. of shaft above the blade in the American instrument is in the writer's opinion a disadvantage as it influences the angle at which the blade can be introduced and makes it more difficult to apply when the head is engaged (See Fig. 3).

3. An ingenious locking mechanism is employed with a sleeve that falls into position automatically as the shaft is straightened. The single joint allows for this shorter locking sleeve

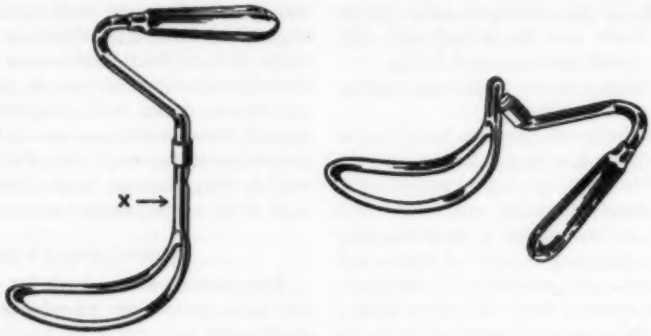

FIG. 2

The Weisman-Carrabba Modification. Note length of shaft above blade marked X.

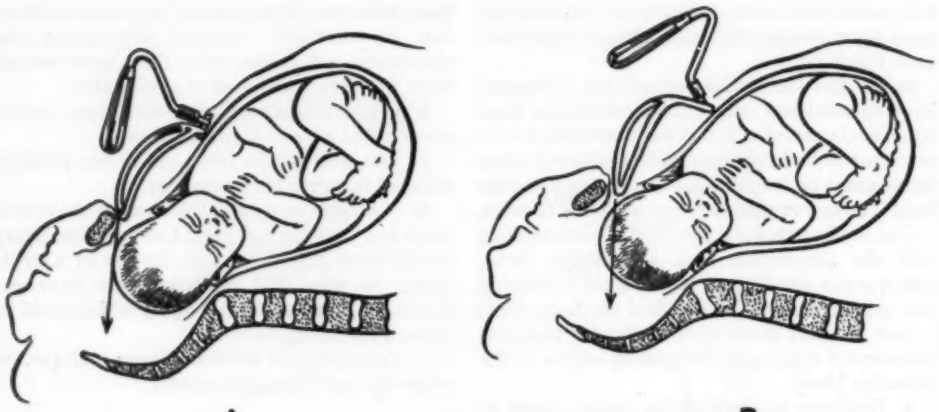

FIG. 3

Showing A Murless head extractor and B Weisman-Carrabba Modification, placed ready for insertion. Note how the longer shaft below the joint in B tilts the instrument and affects the path it will take when inserted.

to be used, reducing to a minimum any chance of the mechanism sticking during operation.

We have tried out this new extractor and find it eminently satisfactory, the only disadvantage being the extra length of shaft above the blade referred to above.

Technique

Detail in operative technique will vary with different surgeons but the head extractor can be incorporated with advantage into most methods in use. It is equally useful with transverse or vertical uterine incisions. Minor alterations in our routine have evolved since the instrument was first used and it may be of interest to recount the most important steps.

1. A gauze roll is used to pack at the sides of the uterus and a self-retaining retractor inserted.

2. The vesico-uterine peritoneal fold is divided. The lower edge of this fold and the bladder are displaced downwards and packed beneath the symphysis with the loose end of the gauze roll which is held down by the assistant's fingers while the uterine incision is made. Bladder retractors of the Doyen's type may impede the easy introduction of the extractor.

3. A transverse incision is made in the uterus centred on the midline and only wide enough to admit the extractor blade.

4. As soon as the incision enters the uterine cavity the lower edge of the wound is grasped with forceps (De Martel's, Green-Armytage or Lane's) and is raised from the foetal head. This is an important step and facilitates introduction of the extractor.

5. The extractor, held in the right hand in the folded position, is placed on the abdomen with both extremities of the curved blade in contact with the tissues (Fig. 3). The blade is now introduced between the foetal head and the raised lower flap of the uterine incision and pushed downwards until it envelops the foetal head.

As it slides round the head the joint extends and when the shaft is straight, it is locked with the sliding collar.

When deep engagement or impaction are present, it is necessary to raise the head before the extractor can be inserted. This is accomplished by inserting two fingers of the left hand into the uterine cavity and pushing the head upwards. While these fingers hold the head, the instrument is introduced between the fingers and the lower flap of the uterine incision and manœuvred into position before the fingers are withdrawn.

6. Ergotrate is injected intravenously as soon as the extractor is in place.

No untoward effects on the foetus, even in cases of foetal distress, have been noted from this practice. Occasionally slight difficulty may be experienced in delivering the shoulders if the uterus is contracting hard.

7. The head is now delivered by the action of the uterus supplemented by fundal pressure and is gently lifted and guided out of the uterus by the Extractor. It will be noticed that the head often rotates so that the smallest circumference engages in the incision.

As the head stretches the uterine wound, this is enlarged sufficiently to allow it to pass, either by lateral scissor snips under direct vision, or by splitting the muscle with the tips of the forefingers.

Delivery should be slow, and strong pulling on the extractor must be avoided.

8. The operation is completed in the usual manner.

Summary

1. The routine use of the foetal head extractor in low Caesarean section is discussed.

While it is admitted the extractor is not an essential instrument, it is claimed that it is a useful addition to the armamentarium and renders the operation easier, safer and neater. Therefore it is recommended that young obstetricians should be trained to use it.

2. Certain criticisms of the instrument are recorded and have been examined. Practice in handling the instrument may be required before its full benefit can be attained in all cases.

3. The original claims made for the extractor remain unchallenged and still hold good after further operative experience.

4. A modification of the instrument is described and its merits compared with the original.

5. A brief summary of the operative technique now used by the writer is given.

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The Murless head extractor is manufactured by Allen & Hanburys Limited, Wigmore Street, London.

The Murless head extractor (Weisman-Carrabba Modification) is manufactured by the Goodman-Kleiner Co. Inc., East 17th Street, New York.

PREGNANCIES IN A CASE OF ENDOMETRIAL TUBERCULOSIS TREATED BY STREPTOMYCIN

BY

YEHUDA M. BROMBERG

AND

SAMUEL ROZIN

From the Gynaecological-Obstetrical Department, Rothschild Hadassah University Hospital, Jerusalem, Israel

ENDOMETRIAL tuberculosis is usually associated with sterility, and only a few cases of intrauterine pregnancy have been reported in this condition (Zondek, 1944; Jedberg, 1950; Schockaert, 1952; Sharman, 1952; Stallworthy, 1952). Sterility of patients suffering from tuberculous endometritis is mostly due to tubal obstruction, but pregnancy occurs only exceptionally, even in those cases in which the tubes are completely or partly patent.

Streptomycin therapy has been applied in the treatment of genital tuberculosis with frequent favourable results as to the endometrial disease, but with no effect on the involved tubes. In a case of endometrial tuberculosis with patent tubes, as reported below, streptomycin treatment was followed by 3 consecutive abortions and 1 ectopic pregnancy.

CASE REPORT

Mrs. J.Z., aged 31 years, married for 3 years, was first examined for primary sterility in January 1947. She had her first menstruation at the age of 13 and continued to menstruate regularly. Her past history did not reveal any serious diseases, and there was no evidence of pulmonary tuberculosis. The patient was apparently a healthy and well built woman, and her only complaint was sterility. Physical examination and X-ray of the chest did not reveal any abnormal findings.

Gynaecological examination showed a long nulliparous cervix and a small hypoplastic uterus (hysterometry 7 cm.), while the tubes and ovaries were not palpable. Hystero-salpingography showed a small, but normally shaped uterine cavity and both tubes patent. Premenstrual endometrial biopsy revealed typical tubercles in the secretory phase of endometrium. The diagnosis of tuberculous endometritis was confirmed by another biopsy performed 2 months later. Treatment with streptomycin, 1 g. daily, was administered for 40 days, during February and March 1948. A thorough endometrial curettage at the conclusion of this treatment and the following numerous serial histological examinations failed to show tuberculous changes in the removed tissue. Five months later the patient was again submitted to streptomycin treatment (1 g. daily for 30 days), followed by endometrial biopsy which again showed no evidence of tuberculosis.

In April 1949 the patient was admitted to the hospital because of profuse bleeding, which occurred 8 weeks after her last menstrual period. A pregnancy test made 2 weeks previously gave positive results. A curettage was performed and placental tissue removed. The histological examination revealed a necrotic chorionic and decidual tissue with no signs of tuberculosis.

Six months later (October 1949) the patient consulted us again, because of a 6-weeks delay in menstruation. The pregnancy test was positive. However, one month later the test became negative, although no uterine bleeding occurred. A diagnosis of missed abortion was made, and the curettage performed showed, at histological examination, necrotic placental tissue.

In February 1951, approximately 1 year after the second abortion, pregnancy occurred again followed by an early abortion at the end of the second month after the last menstrual period. No tuberculous changes could be found in the histological examination of the removed placenta.

During a period of 1 year, which followed the last abortion, the patient was not submitted to any treatment, and consulted us again in February 1952 because of her desire for motherhood. Endometrial biopsy with serial histological examinations and inoculations of endometrium into guinea-pigs gave again negative results for tuberculosis.

On 13th June, 1952, the patient was admitted to the hospital, complaining of severe abdominal pains and vaginal bleeding, which occurred 7 weeks after her last menstrual period. She was very anaemic and had a rapid pulse and low blood-pressure. The pelvic examination was very painful and revealed a swelling behind the uterus. Upon opening the abdomen a considerable

amount of free blood was found in the peritoneal cavity; the right tube, which was greatly enlarged and bleeding freely from a rupture in the isthmic part, was removed. The left tube had a normal appearance and seemed patent. The uterus was normal in size and did not show any abnormalities. Both ovaries also seemed normal. The inspection of the pelvic cavity did not reveal gross lesions characteristic of tuberculosis and no adhesions between pelvic organs. The postoperative course was uneventful. The histological examination of the removed tube showed placental tissue and chronic endosalpingitis. No evidence of tuberculosis could be found in serial histological examinations. Part of the removed tube was inoculated into a guinea-pig and gave negative results for tuberculosis.

Three months after the operation a hysterosalpingography was performed and showed a small-sized uterine cavity with a patent left tube.

Comment

The importance of antituberculous therapy as far as sterility is concerned can be evaluated only on the basis of subsequent pregnancies. It appears that pregnancies, which were very uncommon before the streptomycin era, still remain exceptional (Murray, 1950; Bédrine and Houlné, 1952; Hering, 1952; Rabau, 1952). The rare occurrence of pregnancies in genital tuberculosis despite antibacterial treatment is explained by the obstructed tubes usually found in such patients. Therefore, antituberculous treatment is of special value in the rare cases of tuberculous endometritis with patent tubes. In those cases pregnancy may be expected following treatment, since endometrial tuberculosis can be cured by streptomycin (Seved, Falls and Zummo, 1950).

In the case described above, the histological examinations and the inoculations of the endometrium into guinea-pigs, following streptomycin treatment, showed repeatedly negative results for tuberculosis. Pregnancies followed the recovery of the endometrium from tuberculosis. Although the finding of chronic salpingitis in the removed tube could arouse suspicion of coexistent tuberculous involvement, this was disproved by serial histological examinations.

The repeated abortions in this case could be probably explained by the uterine hypoplasia, usually associated with tuberculous endometritis.

Summary

The story of a patient suffering from sterility due to endometrial tuberculosis and treated by streptomycin is reported. The treatment was followed by negative results for tuberculosis in repeated histological and bacteriological examinations of endometrium. The recovery of the endometrium from tuberculosis was followed by 3 early abortions and 1 ectopic pregnancy.

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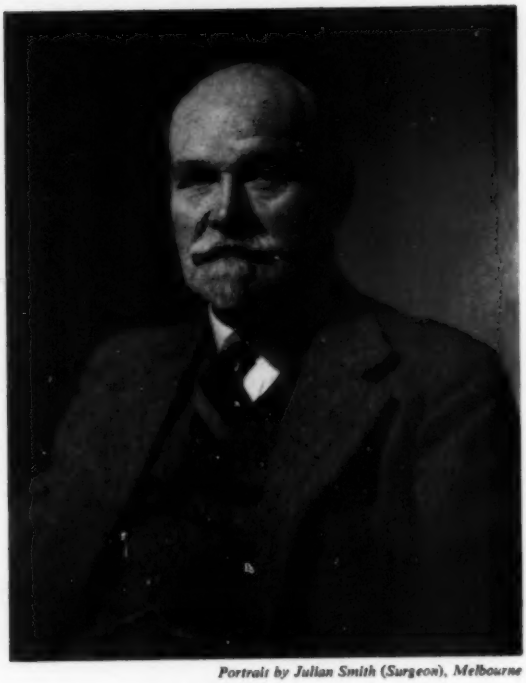

Portrait by Julian Smith (Surgeon), Melbourne

THOMAS GEORGE STEVENS

Obituary

THOMAS GEORGE STEVENS

M.D., M.R.C.P., F.R.C.S., F.R.C.O.G.

It is many years since T. G. Stevens moved amongst his colleagues and friends in the full activity of a consultant's busy life, but his death on November 10th, 1953, aged 84, will have recalled many memories of a vital personality. He was born at Newington Green, North London, where his father was a surgeon, and educated at St. Paul's School and later at Guy's Hospital, where he qualified. He laid the foundations of his clinical career by spending two years in resident posts at Guy's, Evelina and Queen Charlotte's Hospitals. It was the experience of the last appointment, where, in those days, he found a large experience of the serious abnormalities of labour, which determined his interest in and devotion to obstetrics.

The aim of all aspiring consultants and specialists in the nineties and for long after was to build up a private practice, combined with part-time work in hospitals, but it was a slow and gradual process for most of us. To mitigate the difficulties of the waiting years Stevens held the post of demonstrator in biology at Guy's for some years before he was appointed as Tutor to the department of Obstetrics and Gynaecology at St. Mary's Hospital in the early years of the century under Montague Handfield-Jones and W. J. Gow. Those of us who attended his tutorial classes will still remember his simple, clear and dogmatic teaching, exactly what was needed by students who were preparing to face their examiners. His early election to the staff of the Hospital for Women, Soho Square in 1899 was quickly followed during the next ten years by honorary staff appointments to Queen Charlotte's in 1908 and to St. Mary's in 1912 on the retirement of Handfield-Jones. With the unexpected and early retirement of W. J. Gow, two years later Stevens became senior Obstetric Surgeon to St. Mary's, an appointment which he held until his own retirement under the age rule of 65 in 1934.

Meanwhile his practice had grown rapidly and he became one of the busiest obstetricians in London. At Soho he had charge of gynaecological beds which were denied him at his own teaching hospital until 1912 and from then until he became senior in the department he was given no more than token charge in the wards.

Nevertheless, Stevens became an expert operator, quick and sure. He was particularly adept at the various operations for prolapse which he attributed to his tutelage by the Manchester school. To his theatre visitors he appeared to be almost nervously excited, especially during abdominal work, but he seldom made mistakes and always operated with conscientious care. For many years he had charge of 16 beds at Soho and 16 at St. Mary's, a considerable responsibility and physical effort for one who seldom delegated a minor and almost never a major operation. Even at his retirement he was still working to his full capacity in hospital life without apparent undue fatigue; indeed his physical stamina in the theatre was quite remarkable. It was perhaps a just criticism by his juniors that he gave them little opportunity for gaining practical experience. There was not a trace of a jealous grasping of the work for himself. He felt a genuine responsibility for the patient which made him believe that he was failing in his duty toward her if he delegated the operation to his registrar. On those rare occasions when he was persuaded to allow a junior to perform a hysterectomy he would not leave the theatre until the operation was completed.

But while Stevens was a facile gynaecological

surgeon it was in obstetrics that he excelled. In those days skill in "vaginal obstetrics" was gained by much experience of difficult and neglected labour which is almost unknown today. He developed a remarkable skill in manipulation which all those who saw his work at Queen Charlotte's will remember. With this went a shrewd clinical insight into the course of labour which taught him that the majority of women will deliver themselves without harm to mother or baby with time, patience and sedatives. To Stevens "meddlesome midwifery" was anathema.

While many will recall Stevens's clinical knowledge and skill it is probably his teaching which was the most impressive. He never lost his straightforward dogmatic style which is helpful for the undergraduate student. Even towards the end of his career when he had accumulated that wide experience which often influences a teacher away from the precision of the tutor, he retained his simple method, uncluttered by theories for which he had no time until they had become recognized guides to routine practice.

He believed in giving the student a basic learning of sound essentials on which, later, he could build his own impressions. As an examiner Stevens was fair and demanding of no more than an elementary knowledge, but this was a minimum which he rightly expected.

In addition to his busy life in hospital, as an examiner, in private practice and as a member of numerous committees, he found time to publish several successful books. In 1912 he wrote his "Diseases of Women" which was a model of a textbook of those days for the student. If he could have written a similar textbook of obstetrics it would have rivalled Herman's "Difficult Labour" in its value and popularity. He was one of the "Ten Teachers" and contributed various chapters to edited books.

As a speaker at the Obstetric Section and other gatherings, Stevens was typically forthright and uncompromising. He enjoyed twitting his opponents in discussion sometimes with gentle shafts but always with a saving humour which earned him an interested attention.

Stevens was a foundation Fellow of the then British College of Obstetricians and Gynaecologists, but he was never an enthusiastic supporter as he was doubtful at the time of the necessity for founding a third College. He was essentially a man of the problems of the day with no great grasp of the unfolding future. He did not see clearly how the expansion, chiefly of obstetrics in its relation to the wider problems of Public Health, was either near at hand or how the newly-founded College could work for the improvement of maternal and child welfare. Nevertheless he was a member of the first Council for six years, and served on various committees until his retirement in 1934.

Stevens's medical hobby was the histopathology of the pelvic organs, indeed his interest in diagnosis led to a skill which was frequently consulted by his colleagues when confronted with difficult sections.

As a man he had a distinctive personality, which, with its gaiety and joy in fun, appealed to the company of men. There was a sparkle in his eye and smile of welcome on meeting which was immediately attractive to all. In his role of a good friend he was at his best at the meetings of the G.V.S. He was one of the earliest members, if not a foundation member in 1912, and seldom missed a gathering whether at home or abroad. His lively criticizing of the various displays organized by the hosts of the meetings, his witty talk and good stories in a little group around a table all made him one of the most popular members.

But below this side of his personality there was a solid character based on principles of professional honesty, square dealing and the strictest conscientiousness in clinical work. Every patient who was entrusted to his care, whether in private practice or hospital clinic, was "safe" in so far as he would make her an individual responsibility. Perhaps it was his own simple honesty which made him intolerant of humbug and pose in those around him. Seldom did he show anger, but when he met insincerity and prevarication he was impatient and contemptuous.

Stevens made no claim to academic distinction and was suspicious of unproved theories, which ranged beyond the apparently obvious, for he was an essentially practical man, not given to speculation, except within very narrow limits, and unburdened with imagination. For him

imagination was unreliable as a guide to the immediate problems of his daily life.

His chief relaxation was painting. As an amateur he reached a level of facility which was recognized by the selectors of the exhibition of Medical Artists. Out of doors he was a plodding golfer and quite an expert fisherman.

Stevens enjoyed life. It held much for him in the companionship of friends, interest in his work and the pleasure of his amusements.

When he retired from St. Mary's in 1934 he disappeared from London, laid down all his professional responsibilities and went to live in Bournemouth where he enjoyed many years of happy retirement.

He married Lizzie Jane, the eldest daughter of the late John Reeves of Blackheath. He lost her just over a year before he died.

His son, Mr. T. Russell Stevens, is a surgeon on the staff of the Dorchester County Hospital.

ALECK BOURNE

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

AUTUMN EXAMINATION

LIST of Candidates who have been awarded the **Diploma in Obstetrics.**

Charles Alexander Calderwood Abraham.
Richard David Allen.
Joseph Patrick Alvey.
Alan Gerald Amias.
John Allan Dalrymple Anderson.
John Richard Angwin.
James Henry Armstrong.
Robert Bain.
David Alastair Baird.
Doreen Sheila Ball.
Geoffrey Vernon Balmforth.
John Alexander Campbell Bamford.
Arthur Allan Bapty.
Alexander Patrick Barclay.
Neville Howitt Barley.
Hugh Cooper Barr.
Anthony Carlyle Beatty.
Henry Robert Clifford Benny.
William Geoffrey Benson.
John Sanford Berkeley.
Margaret Sarah Beverland.
John Robert Billinghurst.
Dorothy Gladwin Blackett-Ord.
Robert Carnwath Bloomfield.
Desmond Gilliland Bluett.
Audrey Anne Boutwood.
Iona Mary Brereton.
Raymond William Brotherwood.
Bernard Jacques Brown.
Christopher Tibbits Brown.
George Laird Brown.
John David Bruce.
Christopher Vincent Bullen.
Andrew Kennedy Burt.
Seonaid Catherine Cameron.
Patricia Emily Campbell.
Ronald Wilson Campbell.
Reginald Carr.
Sumathi Rebecca Chandy.
Sin Giap Chua.
Bruce Wallis Cole.
Barbara Mary St.John Coventry.
Hubert John Edwin Cox.
George Edward Crawford.
Peter Macdonald Crawford.
Patrick Forsyth Aitken Crawshaw.
Flora Mary Dale.
George Marshall Davidson.
Ian Francis Digby.
Josephine Dolan.
Kenneth Charles Easton.
Barbara Campbell Edwards.
Brian David Ellis.
Doreen Alice Ellis.
Lionel Elton.
Hugh Alexander Evans.
Margaret Griffiths Fairman.
Donald Collins Faull.
L. C. Fernandez.
Frank Irving Firth.
John Anthony Fleming.
Marjorie Hannah Earnshaw Flowerday.
Donald Stewart Foster.
Ian Hutchison Gardner.
William Ainslie Gentle.
William John Glover.
Mervyn Goodman.
Leonora Helen Goulty.
Christopher William Grant.
Monica Cornelia Grant.
Cary Cantle Griffiths.
Jean Millwood Halliwell.
Elinor Catherine Hamlin.
John Langford Hanington.
Maureen Elisabeth Hardeman.
James Gerard Hayes.
Margaret Angela Hayes.
John Hennigan.
John Richard Hewett.
Aaron Nathan Horwitz.
Michael Howett.
John Dill Jackson.
Ronald James Jameson.
Andrew Jervis.
Daniel Derrick Johnstone.
George Murray Johnstone.
Zohra Begum Kazi.
Thomas Waddington Kidd.
Frank Ferguson Kinnaird.
William Arthur Kirkpatrick.
Thomas Paul Kissack.
Ronald Louis Kleinman.
Mukulika Konar.
Yu Shing Lam.
Sheila Mary Lane.
Allan Smith Liddell.
Ruth Lister.
Mary Isabel Lloyd.
Anne Elizabeth Thornton Lodge.
William Harry McBay.
Thomas Donal McCarthy.
Jessie Macdonald.
Morag Stuart Macdonald.
John MacIntosh.
Michael Joseph McKenna.
Alexander Mackinnon.

John Henry Marks.
Helen Frances Martin.
Joseph Barnett Hicks Martin.
Paul Lawrey Martin.
David George May.
Prabha Mehra.
Arnold Henry Mendoza.
Baron Rowley Middleton.
Norman Alfred Miles.
Robert Harvey Douglas Miles.
Andrew Patrick Millar.
Andrew Parker Miller.
Donald Dundas Moir.
Marjorie Monk.
John Langlois Montagnon.
Ronald Dugdale Morbey.
David Frederick Morley.
John David Morris.
Edward Alexander Murray.
Joan Margaret Nabarro.
Shirley Evelyn Nathan.
Rhoderic William Arthur Nel.
Peter Anthony Normandale.
Richard Christopher Norton.
Kenneth Carner Nyman.
Irene Muriel Frances Ondatje.
Heather Maureen Panton.
Edward Rowlinson Parry.
Mary Caffyn Wright Paterson.
David Corah Pattison.
Peter Pau.
Barbara May Philpott.
Allan Clarke Cullen Pinion.
Geoffrey Henry Gibson Poole.
Gertrude Mary Pullan.
Thomas Aneurin Iorwerth Rees.
James Gordon Rider.
Kenneth Jago Roberts.
Charles Rooney.
John James O'Carroll Rorke.
Alfred Derrick Rose.
Leslie Rose.
Donald Percy Rough.
Prokash Chandra Roy.
Francis Clarence Rutter.
Philip Edwin Henry Rutter.
Robin Griffith Seager-Thomas.
Noel Patricia Shannon.
James Sharp.
Mary Eithne Teresa Sheridan.
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Mary Thelma Taylor.
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Barbara Vera Tyman.
Lilian Starr Underhill.
Ian Joseph Waite.
Mary Joan Watson.
John Nicholson Wattie.
Hugh Basil Graham Webb.
Anthony Lethbridge Wells.
William Gilson Wenley.
Thomas Wade West.
Constance Marjorie Wilkinson.
Frank Charles Wilkinson.
Ronald Williams.
Eric Alan Wilson.
Janet White Worling.
Margaret Elizabeth Wort.
Victor Zuck.

A MEETING of Council was held at the College House on Saturday, 30th January, 1954, with the President, Mr. Arthur A. Gemmell, in the Chair.

The following were elected to the **Membership**:

Gordon Todd Dryden Barr.
Desmond John Cassidy.
Vivienne Alice Croxford.
Haider Fahmy Daghistany.
Patrick John Dwyer.
Alfred Leonard Tytherleigh Easton.
David William Somerville Gordon.
Thomas Purdie Grant.
John Greenwell.
Kenneth Greig.
Raymond Wynne Hughes.
George Arnold Humphreys.
Peter Derek Campbell Jackson.
Keith Basil Layton.
Clement Vernon Love.
Arthur Campbell McInnis.
Peter Manolis.
Mrinmoyee Mukerji.
Francis Anderson Murray.
Robert Finbarr O'Donoghue.
George Douglas Pinker.
David Edmund Savage.
Satwant Ganda Singh.
Hugh James Tighe.
John Reuben Dacomb Tomlinson.
Alexander Cuthbert Turnbull.
Rama Vaish.
Peter Sherratt Watson.
Victor Thompson White.

REPORTS OF SOCIETIES

NEWCASTLE UPON TYNE OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

October 1953

A meeting of the Newcastle upon Tyne Obstetrical and Gynaecological Society was held in the Royal Victoria Infirmary on 8th October, 1953.

The President, Dr. Hendry, was in the Chair.

Mr. Charles Read gave an address on

Pelvic Exenteration

The operation involved one of three procedures. Either an anterior exenteration in which the ordinary extended Wertheim's operation is performed but in addition the bladder is removed and the ureters transplanted into skin or some part of the intestinal tract. The second procedure, a posterior exenteration involved the ordinary combined abdomino-perineal excision of the rectum combined with hystero-vaginectomy and a lymph node dissection. The third type of operation, the total exenteration as practised by Brunschwig, consisted of total pelvic evisceration with or without removal of the vulva at the same time. Mr. Read was of the opinion that the operation was justified on two grounds. In the first place, up to 30 per cent of patients dying of cancer of the cervix die with the disease still localized to the pelvis. In the second place the alternative to the operation is death. The ultimate success of the operation depended upon careful choice of suitable cases by an operator fully trained in ultra radical surgery. Mr. Read believed that there was little place for palliative pelvic exenteration; where there was evidence of metastases outside the pelvis the operation ought not to be performed. The following conditions must be fulfilled before pelvic exenteration is performed.

(1) Advanced pelvic cancer uncontrolled by irradiation. (Exceptions to irradiation are advanced primary carcinoma of the ovary, vulva, rectum and bladder.)
(2) Disease localized to the pelvis—clinical and X-ray evidence.
(3) Reasonable renal efficiency. (Blood urea and intravenous urography.)
(4) The patient's general condition is such that she may reasonably be expected to survive after the operation.

Mr. Read dealt with certain technical points in the operation.

1. *Anaesthesia.* Pentothal followed by gas and oxygen with a relaxant such as tubo-curarine was the anaesthetic of choice; he did not favour the use of hypotensive drugs.

2. *Blood loss.* In all cases a drip transfusion of blood was given during the operation and every effort was made to avoid blood loss. As soon as the abdomen was opened the internal iliac artery on either side was tied off; during the operation great care ought to be taken to ensure good haemostasis. The diathermy was a most useful instrument in drying up the walls of the cavity left after the operation. Mr. Read emphasized that many of the patients developed a haemolytic type of anaemia after this operation and it was important to check haemoglobin levels during the first 10 days of the convalescent period.

3. *Wet colostomy.* In a patient who is to have a wet colostomy it had been found helpful to excise the umbilicus as the suspension of a bag below the umbilical level was found by many patients to be irksome and uncomfortable. If the colostomy can be brought out high up, then it is much more tolerable. It was important that the colostomy should project about 1 inch into the colostomy bag; this resulted in much better skin hygiene around the colostomy.

4. *Uretero-intestinal anastomosis.* The simplest method of uretero-colic anastomosis was considered the best as this has to be performed at the end of a long tedious operation. Mr. Read favoured the short Coffey anastomosis, but occasionally he performed a direct stab implant.

5. *Lymph Nodes.* A block dissection of common, internal and external iliac and obturator nodes was made during the operation. If the inguinal nodes were to be removed it was better to do so a few weeks after the major operation.

6. A careful examination of the abdominal cavity should be made in all cases before embarking on such an extensive operation. Distant metastases were a contra-indication so far as pelvic exenteration was concerned.

7. The importance of the electrolyte balance in the post-operative period was discussed; particularly this applied to sodium-potassium balance.

Mr. Read then reviewed the 38 cases which he had operated on up to that date; there had been 7 post-operative deaths in the series. He did not think it possible to lower the operative mortality below 15 per cent because the death rate from transplant of the ureters alone was 12 per cent. The first patient to be operated upon would soon reach the 5-year post-operative stage and at the moment her general condition was satisfactory. Mr. Read stressed the necessity for a large series of cases before any conclusions could be drawn.

Complications of the Operation

In Mr. Read's experience few patients who have undergone this radical operation have suffered from deep shock, and oliguria and anuria associated with shock have not been such a problem as he had anticipated. Where oliguria or anuria have occurred the cases have been treated by the regime outlined by Bull.

Ureteric obstruction may occur following transplantation of the ureters; some operators have advised indwelling ureteric catheters but Mr. Read had had no experience of this treatment.

The main serious complications peculiar to this operation were: (1) urinary leakage, (2) intestinal fistulae, (3) pyelitis and (4) nerve injury. A number of minor complications such as vulval discharge or irritation round the site of the wet colostomy could be troublesome.

Mr. Read showed photographs of a number of specimens which he had removed. In conclusion he restated his belief that this operation had a place in the treatment of advanced cancer of the cervix where the growth was confined to the pelvis. He was firmly convinced that the patient with extra-pelvic metastases should not be subjected to the operation, with the possible exception of the case where there was a double vaginal fistula. This complication of carcinoma of the cervix caused great distress and if the patient were in good condition pelvic exenteration might be considered as a palliative measure.

HOSPITAL REPORTS

BY

ANTHONY W. PURDIE, M.B., F.R.C.O.G.

BROMLEY GROUP HOSPITAL MANAGEMENT COMMITTEE. MATERNITY CLINICAL REPORT FOR 1950

THIS is a Group report from three hospitals, Beckenham Maternity Hospital, Farnborough Hospital and Bromley Hospital. Previously Bromley Hospital has issued several annual reports but this is the first combined report from the Group. The report follows that recommended by the Royal College of Obstetricians and Gynaecologists with a few minor modifications. In the opening survey there is a section explaining the circumstances peculiar to each of the individual hospitals. In the preambles to the individual tables the different methods of treatment adopted in each of the hospitals are indicated and in the tables themselves it can be seen clearly at which hospital each individual case was treated. Yet the data from each hospital have been integrated into a single and harmonious report.

The report deals with the particulars related to 3,378 deliveries which took place in the hospitals concerned; 94 per cent were booked and 6 per cent non-booked. There was not a single maternal death. The stillbirth rate was 28·5 per 1,000 total births and the neonatal death rate 14 per 1,000 live births. Perusal of the report shows a high proportion of abnormal cases, and it must be a source of satisfaction to all concerned that this carefully prepared combined report should be the record of a highly successful year's work.

REGISTRARS' REPORT, LIVERPOOL MATERNITY HOSPITAL FOR THE YEAR 1950

DURING the year there were 2,567 hospital deliveries with 2 maternal deaths. The stillbirth rate was 31 per 1,000 total births, and the neonatal death rate 15 per 1,000 live births. The first maternal death occurred in a patient still under anaesthesia at the end of an otherwise uneventful repeat Caesarean section; autopsy showed acute congestion and oedema of both lungs. In the second fatal case death occurred from congestive heart failure in a patient suffering from chronic rheumatic carditis 12 days after delivery by Caesarean section. In this case death would appear to have been unavoidable.

The operative rates reflect a tendency to early interference, the incidence of Caesarean section being 13·2 per cent and that of forceps delivery 17·6 per cent; their corrected respective foetal mortalities are 3·5 per cent and 2·6 per cent. It is interesting to note that in 70 uncomplicated breech deliveries forceps was applied to the after-coming head on 52 occasions; there were no stillbirths in these 70 cases and only 2 (2·8 per cent) neonatal deaths.

The paediatric section of this report is both extensive and comprehensive.

CLINICAL REPORT OF THE CRESSWELL MATERNITY HOSPITAL, DUMFRIES FOR THE YEAR 1951

THE number of patients treated during the year was 1,781 and among these the total number of deliveries, exclusive of abortion, was 1,425. There was not a single maternal death during the year. Yet there was no lack of complicated cases; we find, for example, 98 cases in the hypertensive toxaemic group, 8 cases of eclampsia, 38 of antepartum haemorrhage, 40 of postpartum haemorrhage, 42 of contracted pelvis to cite but a few instances. There were 44 stillbirths (3·03 per cent) and 35 neonatal deaths (2·48 per cent). The Caesarean section rate was 2·6 per cent and the forceps rate 7·0 per cent. The Staff is to be congratulated on an excellent year's results.

CLINICAL REPORT OF THE MATERNITY DEPARTMENT, PADDINGTON HOSPITAL, LONDON, FOR THE YEAR 1951

THERE were 2,132 adult patients admitted during the year to the modern maternity wing of this general hospital. The wing contains 72 lying-in, 15 antenatal and 11 labour ward beds, with a premature baby unit of 8 cots. There were 1,981 deliveries (1,872 booked and 109 non-booked), with 2 maternal deaths. The first of these deaths due to coronary artery thrombosis and cerebral embolism occurred 13 days after delivery, while the second due to acute haemorrhagic pancreatitis occurred after slow deterioration some 7 weeks following delivery. Each appears to have been an unavoidable death. The stillbirth rate was 22·4 per 1,000 total births, and the neonatal death rate 17·3 per 1,000 live births.

In the "toxaemic" table an attempt is made to divide the cases up exactly into cases of preeclampsia, pre-eclampsia without albuminuria, essential hypertension without superadded preeclampsia, essential hypertension with superadded preeclampsia, and chronic nephritis—a difficult task and not all would agree with the criteria chosen.

The operative interference rate reflects a conservative practice, the forceps rate being 3·9 per cent and the Caesarean section rate 2·9 per cent. Of the 56 Caesarean sections performed 16 (29 per cent) were classical and 40 (71 per cent) lower segment operations. Among the

cases of special interest are one successful Caesarean hysterectomy for rupture early in labour of a previous classical Caesarean section scar, one of successfully treated severe oliguria following concealed accidental haemorrhage and postpartum haemorrhage, and one of recovery following operation in a new-born infant for congenital oesophageal atresia with tracheo-oesophageal fistula.

This is the Department's second annual report and is the record of a most satisfactory year's work.

CLINICAL REPORT OF THE MATERNITY UNIT, WEST HILL HOSPITAL, DARTFORD, KENT FOR 1952

THE department is a separate unit in a general hospital serving a mixed area of dense suburban, industrial and scattered rural populations. This is the department's first published report and follows the lines recommended by the Royal College of Obstetricians and Gynaecologists.

The number of beds in this unit is not stated but it is said to receive all emergencies as it is the only specialist unit in the neighbourhood, in fact no emergency has ever been refused. During the year 1,122 deliveries (exclusive of abortions which are admitted to the gynaecological ward and are not included in this survey) took place in the unit. There were almost equal numbers of primigravidae and multigravidae. The incidence of non-booked patients is only 6 per cent, but this low figure is considered to be largely technical as the local practitioners are encouraged to refer doubtful cases for opinion before the onset of labour and do so.

There was not a maternal death during the year. The stillbirth rate was 26 per 1,000 total births and the neonatal death rate 35·8 per 1,000 live births. The department is to be congratulated on its first reported year's work.

CLINICAL REPORT FOR 1952, MATERNITY DEPARTMENT, OUR LADY OF LOURDES HOSPITAL, DROGHEDA

THE maternity department has 50 beds of which 6 are antenatal, 42 postnatal and 2 isolation. There were 1,301 deliveries (which probably include 74 abortions although this is not clearly stated) in the intern service and 42 in the extern service. There was 1 maternal death from eclampsia. This patient, a booked case, failed to attend the antenatal clinic at the 37th week as asked to do, and was admitted at the 38th week with severe preeclampsia, had 1 fit and died some 4 hours later with clinical signs of cerebral haemorrhage; permission for autopsy was refused. There were 34 stillbirths (16 macerated) and 24 neonatal deaths in the hospital, 1 stillbirth and 1 neonatal death on the district. Post-mortem examination on these infants was the exception rather than the rule owing to difficulty in obtaining permission. The Caesarean section rate was 1·8 per cent, and the forceps rate 5·5 per cent. Symphysiotomy was performed on 6 occasions for contracted pelvis; 5 infants survived, but 1 died in white asphyxia 1½ hours after birth.

CLINICAL REPORT OF THE ROTUNDA HOSPITAL, DUBLIN FROM 1ST NOVEMBER, 1951 TO 7TH NOVEMBER, 1952

THIS report covers the last year of the late Dr. O'Donel Browne's Mastership, and has been compiled by Dr. Ninian Falkiner who was in charge of the hospital from the Master's death until the election of the new Master some months later.

The letterpress of this report has been limited in view of the very full report of the previous year containing the explanations of the various lines of treatment adopted. The 52 pages of the present report are crammed with a wealth of valuable statistical material. Many tables give 5-year surveys of the principal pregnancy complications and their treatment and 5-year surveys of obstetric operations and their results.

The report which is full and comprehensive, modest in its statement of successes, frank and impartial in its criticism of deficiencies, deserves detailed study. Its crowded pages are a worthy tribute to the memory of a great Master.

CLINICAL REPORT, COMBE LYING-IN HOSPITAL, DUBLIN FOR THE YEAR 1952

DURING the year there were 2,085 deliveries and 165 abortions in the Intern Service, and 1,440 deliveries and 311 abortions in the Extern Service. Including abortions, therefore, 4,001 women were delivered under the hospital's care during the year. There were 7 maternal deaths in the hospital and none on the district. The considered opinion in the hospital is that of these deaths 2 were definitely avoidable, 2 probably avoidable, 1 doubtfully avoidable, while 2 were apparently unavoidable.

Dealing with the Intern figures we find 2,132 total births (exclusive of abortions), 102 stillbirths (48 per 1,000 total births) and 61 neonatal deaths (30 per 1,000 live births).

There is a vast amount of information in this meticulously prepared report which deserves careful study. Nowadays we are becoming accustomed to excellent results from maternity hospitals. But a great deal of care and co-operation on the part of many people is necessary to achieve, maintain, and improve still further these results. The following quotation from this report is a timely warning against complacency. "Recent statistics have quite clearly indicated that one-half of maternal fatalities, one-half of foetal deaths and much immediate and remote puerperal morbidity are entirely avoidable. Efficient antenatal care provides the first and most important means of effecting this saving of life and health. Even nowadays, many pregnant women are unaware of the advantages of antenatal care, or even of the very existence of such a service. With respect, it may be stated, too, that some doctors and nurses are not familiar with a system of adequate antenatal supervision. Recently-qualified medical men, students and probationer midwives will appreciate, therefore, the desirability of setting themselves a high standard in this important service to young women and babies. If antenatal care is undertaken at all, it should be thorough, because casual and infrequent examinations give a false sense of security."

BOOK REVIEWS

"Klinische Voriesungen" (Clinical Lectures). By Professor Dr. H. C. WALTER STOECKEL. Pp. 75. Georg Thieme, Stuttgart, 1953. Price D.M.5.70.

THIS book, written at the instigation of Professor Stoeckel's former pupils and dedicated to the gynaecologists of the future whom the author could no longer teach is a random collection of four lectures; one on an obstetrical subject—premature separation of the placenta; one on a gynaecological problem—the fight against malignant disease; one on a joint urological and obstetrical theme—pyelitis of pregnancy, and the last one on conception and sterility, a subject which Professor Stoeckel intended for students of all academic faculties. But there is much more to the book than the enumeration and discussion of medical facts. It is a book written at the end of a rich medical career by a man who not only commands a wealth of knowledge and experience but who also has acquired wisdom, kindness, and understanding. No one will fail to read this book without a tear in his eye and without feeling truly grateful to Professor Stoeckel as a gynaecologist and as a humanitarian. For no one is the dictum that only a good man can be a good doctor truer than of Professor Stoeckel. This little volume of 74 pages truly mirrors the writer and his life dedicated to patients and pupils and one feels deeply stirred long after reading it. *E. Wachtel*

"The Obstetrical Forceps." By L. V. DILL, M.D., F.A.C.S. Pp. ix + 156, with 86 illustrations. Charles Thomas, Springfield, Illinois, U.S.A. (American Lecture Series). Dist. in Great Britain by Blackwell Scientific Publications, Oxford, 1953. Price 37*s*. 6*d*.

THIS beautifully compiled monograph, which is intended as an adjunct to practical teaching for all who practise obstetrics, traces the origin and development of the obstetric forceps and gives details of how they should be applied and used as instruments of rotation and traction. Separate short chapters devoted to each of the forceps of Tarnier, Kielland, Barton and Piper include a description of the instruments, their particular indications, as well as a detailed account of the techniques of their use. Considerable attention is paid to the choice of a pattern of forceps to suit special circumstances with emphasis on the "fit" of the forceps to the foetal head. Controversial issues are occasionally glossed over and sometimes neglected completely. The opening paragraph on "Failure of Rotation", for example, reads: "Today the well equipped obstetrician calmly makes the diagnosis of vertex, occiput posterior, calls for the forceps of his choice, rotates the head without difficulty and delivers the baby. But it was not always so!" Indeed, is it so yet? The only reference to failed forceps is: "The most obvious point made in reports of failed forceps which still appear is the part played by poor judgment, neglected labours, and poor technique."

The scope of the book is probably too extensive for its size but its magnificently illustrated and forthright chapters offer a fund of valuable information for student, practitioner and specialist alike.

"Gynaecological and Obstetrical Anatomy and Functional Histology." By C. F. V. SMOUT, M.D., M.R.C.S., and F. JACOBY, M.D., Ph.D. Third edition. Pp. vii + 336, illustrations 185. Edward Arnold & Co., London, 1953. Price 35*s*.

FOR its third edition the authors have again changed the title of this popular book. This is mainly to emphasize the inclusion of the dynamic histology of the female reproductive system and its endocrine control. After a brief historical review entitled "Milestones in Midwifery" the whole structure of the female reproductive system from the bones and joints of the pelvis to the innervation of the viscera, is built up graphically and logically. There are additional chapters on the placenta and the anatomy of the foetus. All phases of female life, including pregnancy, are dealt with, and the arduous tasks of linking histological appearances with hormone function and of correlating experimental work with clinical observations in this field are admirably and successfully executed within the compass of only a few chapters. While placing emphasis throughout on the practical implications of their subjects, the authors introduce many interesting aspects which seldom find a place in the ordinary textbooks. The sequence of events in follicle atresia; the anatomy of prolapse; and the innervation of the bladder and physiology of micturition are only three of numerous such examples.

For reasons of economy coloured plates have been discarded but the fine quality and overall excellence of the illustrations more than compensates for their omission. Each chapter is followed by an extensive although carefully selected list of references to the relevant literature.

This is an account of applied anatomy and functional histology of the reproductive system presented in a lucid, readily assimilable, and generally acceptable form for all who practise obstetrics and gynaecology. It should be particularly valuable to all who are preparing for higher examinations in these subjects.

"Anoxia of the New-born Infant." A symposium organized by The Council for International Organizations of Medical Sciences. Pp. xv + 230. Oxford: Blackwell, 1953. Price 27*s*. 6*d*.

THE introduction to this book rightly forewarns that this is no comprehensive monograph, but presupposes a knowledge of earlier studies by men such as Barcroft, Windle and Clement A. Smith. Nevertheless a wide field is surveyed from many angles by the 17 participants, drawn as they are from clinicians and research workers in

the related fields of anatomy, physiology, biochemistry, pathology, obstetrics and paediatrics. The personal contributions from Britain by Kenneth Cross, G. F. Gibberd, A. R. Macgregor, T. E. Oppé and James Walker maintain the high standard of exegesis and discussion evident throughout the symposium, which is centred on anoxia as a primary cause of foetal and neonatal death. In turn, the foetal tolerance to anoxia, the establishment of respiration at birth, the state of the brain, circulation and lungs at birth, the maintenance of oxygenation and the prevention and treatment of anoxia are discussed.

This book therefore serves several purposes: it throws light on such dark corners as, for instance, the importance of foetal anoxia in postmaturity and in delivery by Caesarean section; it provides a basis for the substitution of rational procedures for empiricism as, for example, in oxygen therapy; and it shrewdly indicates that the abandonment of the traditional vigorous handling of the newborn will be in vain if it is replaced by injurious instrumentation or injudicious stimulation by machines, however ingenious or intricate. At the same time there is no claim that all problems have been solved, and matters such as the consequences of inhalation of liquor amnii, and the pathogenesis of the so-called hyaline membrane still require further research.

But this publication by virtue of its character, not its content, raises another issue. The symposium restricted to a small number of active and expert participants has several advantages over the larger and hitherto more fashionable congress. These advantages of informality and flexibility are particularly enjoyed in the discussions because they allow a more intimate crossfire of question and answer, of explanation and expiation. But the value of symposium and congress alike is enhanced if as short an interval as possible elapses between the spoken word and the printed report. It is unfortunate therefore that almost 2 years have intervened between the holding of the symposium and the publication of this book in September, 1953. Indeed, in the interval some of the participants have published further reports in the fields covered. The solution to the hiatus is surely to arrange beforehand to publish the proceedings of any symposium or congress in a current journal within 3 or 4 months. The general adoption of such a policy would do much to ease the strain not only on the reader's time and memory but also on his pocket.

"Applied Cytology." By G. R. Osborn. Photography by J. S. Fayers. Butterworth & Co, Ltd., London, 1953. Pp. xi + 168. With 131 illustrations. Price 35*s*.

This is the first British book on cytology, written exactly 10 years after Papanicolaou and Traut published their standard book on Uterine Cancer Diagnosis by the Vaginal Smear. Since then the field of cytology has been widely extended and Dr. Osborn gives an admirably well written and critical survey of the role played by cytology in cancer diagnosis and detection. He describes the cellular patterns found in healthy subjects, in patients with inflammatory disorders and in cancer patients. These descriptions are well supported by most illustrative diagrams and really excellent photomicrographs. The chapters dealing with the normal and pathological cytology of the genital tract, subjects which have been explored by many research workers of all nationalities, naturally form the main part of the book. There are, however, also valuable chapters on the cytology of the sputum, the breast, the urine and pleural and ascitic fluids with an appendix dealing with the laboratory techniques in use for fixing and staining of smears.

Many books and articles on cytological cancer detection have been written within the last 10 years. To Dr. Osborn goes the credit of having approached the subject as a pathologist, and of having correlated histological with cytological appearances. It is to be hoped that his book will be read widely by pathologists and that it will help to convince them that cytological investigation is a valuable though not infallible aid in cancer diagnosis. The student interested in the subject will enjoy this book and find it most helpful in teaching him the essential features of cyto-diagnosis by word and illustration.

"Textbook for Midwives." By Margaret F. Myles. Pp. xii + 676. With 380 illustrations, some in colour. E. & S. Livingstone Ltd., Edinburgh, 1953. Price 42*s*.

This book, written by an outstanding teacher of midwives, and emanating from one of the greatest maternity hospitals in the world, is a sheer pleasure to read. Here is all of value in the lore of the old midwife blended with the knowledge of her modern representative and producing a harmonious union of all that is best in Scottish midwifery. It has been so often true that senior midwives have not been able, for varying reasons, to record in writing the wisdom born of their experience, and especially with regard to special nursing techniques the finer points have been passed on from one generation to another largely by precept and word of mouth. Now at last it has been done, and the result is a book which is eminently satisfying in its material, its presentation, and its illustration. At the end of each chapter there are specimen questions set by the Central Midwives Board and its Scottish counterpart, which provide a good way of "shaking down" the subject just dealt with. The index is good, and the production of the book admirable.

This book will be of great value to the midwife, the pupil midwife, and also to the obstetrician, and Mrs. Myles has every reason to be proud of it.

REVIEW OF CURRENT LITERATURE

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PREGNANCY

1. Serum Protein Levels in Normal Non-pregnant and Pregnant Women.

By B. LIDDELOW. *Med. J. Aust.*, 2, 332-334. Aug. 29, 1953. 2 figs. 4 refs.

This is an attempt to find normal values for serum protein concentration. At the Women's Hospital, Melbourne, serum protein estimations were made in each month of pregnancy on about 20 normal women and on 23 normal non-pregnant women. In these investigations a 3-hour digestive period was used for all estimations of protein by the Kjeldahl method.

Comparing the results with those of Plass and Mathew (1926) the author found that they were of the same order namely, 7 grammes per 100 millilitres of serum in the non-pregnant state and of a lower concentration namely, less than 6·5 grammes per 100 millilitres of serum in the last 7 months of pregnancy.

S. Devenish Meares

2. Amino-acid Metabolism in Pregnancy. Investigation by Paper Chromatography. (Métabolisme des acides aminés pendant la grossesse et son appréciation par la chromatographie sur papier.)

By K. MOGHISSI. M.D. Thesis. Univ. Geneva. 1953. 10 figs. 92 refs.

In this paper some problems of amino-acid metabolism during pregnancy have been investigated using paper partition chromatography.

The first part is a general review of the metabolism of amino-acids both during pregnancy and in non-pregnant women, particular emphasis being placed on amino-aciduria in normal and pathological conditions. Histidinuria of pregnancy is discussed in a separate chapter.

The clinical remission of rheumatoid arthritis during pregnancy is well known. It has been noticed that similar improvement induced by the administration of ACTH and cortisone produces an increased excretion of amino-acids in the urine. These observations prompted the investigation of the amino-acid content of the urine during pregnancy. With this aim the urinary amino-acid excretion of 30 normal pregnant women from 8 to 40 weeks' gestation was estimated. As a control similar readings of the urine of some non-pregnant women were done.

By direct measurement of amino-acid nitrogen as well as by chromatography there was found to be a considerable increase in aminoaciduria during pregnancy, reaching its maximum during the second trimester. In particular it was found that not only did the excretion of amino-acids normally in the urine rise but others such as phenylalanine, tyrosine, and lysine, usually considered pathological, appeared also.

The importance of histidinuria as a test of pregnancy has been emphasized by other writers. Of 30 cases investigated 27 showed the presence of histidine in the urinary chromatogram. This was at its quantitative maximum, as in the case of the other amino-acids, in the second trimester of pregnancy.

During the early post-partum period (4 cases) there was disappearance of abnormal urinary amino-acids and general diminution of aminoaciduria and histidinuria. Aminoaciduria decreased in a case of incomplete abortion.

Absence of histidine and presence of a large amount of phenylalanine and the "nephrosis peptide of *Dent*" characterized respectively the urine of two cases of toxaemia of pregnancy.

The blood amino-acids of pregnant women were found to be nearly the same as those of non-pregnant women.

Comparing the amino-acids of blood and urine it was noted that some of them, e.g., histidine and phenylalanine, excreted in urine during pregnancy are not found in the blood at the same time. In contrast others such as leucines and aspartic acid, although seen frequently in the blood, only rarely appear in the urine.

Comparing the bloods of the mother and the foetus it was seen that both contain the same amino-acids in the same proportions but sometimes those of the foetus are in a slightly higher concentration.

The possible cause of aminoaciduria of pregnancy and its relation to increased adrenal-cortical-like activity has been discussed in the light of these results and those of previous workers in this field.

Author's summary

3. The Experimental and Clinical Significance of Chorionic Gonadotrophin Assays.

By J. A. LORAINE. *Ann. chir. gynaec. fenn.*, **42**, 129-140, 1953. 34 refs.

Various methods of assay of gonadotrophin are discussed and that based on the alteration of prostatic weight of rats was considered to be the most suitable and accurate. In the first trimester of normal pregnancy urinary C.G. was 20,000 to 50,000 units, dropping in the second and third trimesters to 4,000 to 11,000 units. Blood and urinary C.G. were significantly higher in severe toxaemia but there was no change in hypertension of pregnancy or in moderate degrees of toxaemia. Routine assay would be of no clinical assistance in the management of toxaemia. A proportion of diabetics showed a high urinary and serum C.G. but only 25 per cent as compared with 75 per cent in Priscilla White's figures. There was no evidence that a rise in C.G. heralds an obstetric disaster. Foetal death is just as likely to occur when the C.G. is within normal limits. The mean renal clearance of C.G. was not depressed by prolonged oestrogen therapy and was less than 1·0 ml./minute. It was significantly diminished in severe pre-eclamptic toxaemia.

D. M. Sheppard

4. Cerebral Haemorrhage as a Complication in Toxaemia of Pregnancy.

By P. A. JARVINEN and E. HUHMAR. *Ann. chir. gynaec. fenn.*, **42**, 184-193. 1953. 25 refs.

In the first and second Helsinki women's clinics between 1926 and 1950 the incidence of eclampsia among all cases of delivery was 0·34 per cent and the mortality rate of eclampsia was 11·5 per cent. Sixty-two patients died from eclampsia but only 20 postmortems were performed. Of these 20, 12 showed gross cerebral haemorrhage as distinct from petechial haemorrhage characteristic of eclampsia. Six of these cases had had eclampsia with fits, 3 had had eclampsia without fits and 3 had been diagnosed as subarachnoid haemorrhage complicating toxaemia. Five were primiparae and 7 were multiparae. All had been admitted suffering from severe toxaemia and all the multiparae had had toxaemia with previous pregnancies. The symptoms included those of hemiplegia and various nerve palsies.

D. M. Sheppard

5. A Summary of all Cases of Ante-partum Haemorrhage in the Public Section of the Brisbane Women's Hospital during the Period from July 1st, 1951 to June 30th, 1952.

By J. F. DUNKLEY and R. THATCHER. *Med. J. Aust.*, **2**, 93-94. July 18, 1953.

There were 48 patients suffering from significant antepartum haemorrhage among 3,165 admissions. No mother died. The criteria for the diagnosis of placenta praevia were palpation, or direct vision of the placenta at operation, or evidence of separation of the border of the placenta in close relation to the hole in the membranes after delivery.

The 4 central and 4 marginal placentae praevia were treated by Caesarean section except in 1 case where the membranes were deliberately ruptured.

Of the 11 cases of lateral placenta, 3 were treated by artificial rupture of the membranes during labour, and in 8 spontaneous labour and delivery were allowed.

Toxaemic antepartum haemorrhage was encountered 17 times and was generally treated by induction of labour. The rest, that classified as traumatic antepartum haemorrhage and that due to other causes, either delivered themselves or were delivered after artificial rupture of the membranes. For placenta praevia active interference was avoided unless dangerous haemorrhage was continuing or unless the gestation period was longer than 36 weeks and it was suspected that the placenta was central.

Vaginal examinations were done only by the visiting obstetricians and not as a rule in the operating theatre.

In all patients with toxaemic antepartum haemorrhage, who did not begin labour spontaneously within 48 hours, the membranes were ruptured deliberately.

S. Devenish Meares

6. Vaginal Ulceration due to Potassium Permanganate.

By E. A. J. ALMENT and C. S. NICOL. *Brit. med. J.*, **2**, 759-760, Oct. 3, 1953. 9 refs.

Four cases are described of vaginal bleeding due to the insertion of potassium permanganate tablets for the purpose of producing a criminal abortion. All women were pregnant, the maturity varying between 5 and 24 weeks, and the loss was heavy, though not sufficient to warrant surgical control or blood transfusion which has sometimes been necessary in some of the other cases reported in the limited literature on the subject. Two cases showed the typical circular apposition ulcers in the vagina and in a third there were cervical ulcers. The diagnosis usually rests in finding such lesions in the lower genital tract with the remains of a tablet or brownish-black debris of manganese dioxide still in situ. No ulceration was seen in the fourth case described but she presented within 24 hours of insertion of the tablets which she admitted. Tests for syphilis were negative but the authors point out how easily permanganate ulceration may be confused clinically with a chancre if the true history is concealed, especially if the patients present at a special treatment centre as actually happened in 2 of these 4.

Potassium permanganate is readily obtainable at chemists and is commonly used as an abortifacient though it seems that the pregnancy is not affected and the ulcers soon heal.

An addendum to the paper describes briefly heavy bleeding needing ligation of a large vaginal artery following insertion of the tablets by a woman who feared pregnancy.

Doreen Daley

7. Vaginal Bleeding Due to Potassium Permanganate.

By E. E. PHILLIPP. *Lancet*, **2**, 1278-1280. Dec. 19, 1953. 1 fig. 11 refs.

The author records 11 cases of vaginal bleeding following the insertion of potassium permanganate into the vagina during the years 1951-53. A further 4 cases are reported in an addendum to the article. The case histories of 6 of the patients are briefly outlined.

This series of cases resulted from the local belief that potassium permanganate tablets or crystals could bring about abortion when inserted into the vagina. It is thought that potassium permanganate in contact with the moist vaginal wall is broken down into potassium hydroxide and manganese oxide or oxides. The potassium hydroxide causes deep ulceration with bleeding which may at times be dangerous. Treatment consisted of washing away any remaining potassium permanganate and arresting the bleeding, usually by stitching. Attention is drawn to the fact that healing may be accompanied by thick scarring.

H. H. Fouracre Barns

8. Rhesus Investigations at the Utrecht University Clinic for Obstetrics.

By J. LEYNS and J. H. J. BAKKER. *Gynaecologia, Basle*, **136**, 193-202. Oct. 1953.

In 5,773 pregnant women examined between 1st October, 1948 and 31st December, 1951, 4,829 were Rhesus positive and 944, or 16·4 per cent, Rhesus negative. Of the 944 Rhesus negative women, 54 or 5·7 per cent, were found to be immunized, representing 0·94 per cent of the total sample. Of these 52 were group rr (cde-cde) and 2 were R″r (cdE-cde). The titre of immune bodies was determined but it was found impossible to correlate the titre with the severity of clinical changes found in the offspring.

Of the 54 immunized women, 50 were delivered normally, 3 miscarried and 1 had an immature foetus. There was 1 set of twins so that 51 infants were born. Of these 8 were stillborn and 2 died shortly after birth. There were thus 41 healthy neonates: exchange transfusion was given in 13 cases and all these infants survived. Male donors were used exclusively.

Comment. The chief value of this study is the fact that it gives a statistical account of the prognosis for the children of Rhesus negative women. More studies of this kind should be encouraged as only too often the mother is given a gloomy prognosis and suffers unnecessary alarm and anxiety simply because she is told that she is Rhesus negative.

Josephine Barnes

9. Pregnancy and Gaucher's Disease.

By Y. M. BROMBERG, R. TOAFF and D. DIENGOTT. *Brit. med. J.*, **2**, 761-763. Oct. 3, 1953. 2 refs.

Gaucher's disease is a rare condition but it affects women more than men and has a special predilection for the Jewish race so that the authors were able to collect records of 13 pregnancies in 7 women who had attended their hospital in Jerusalem. Nine proceeded to term but 4 pregnancies were terminated in the first trimester for fear that serious risks were involved. No evidence was found to substantiate such fears, for the women allowed to continue did well obstetrically and there was no tendency to haemorrhage or other complications. The disease did not appear to be adversely affected by pregnancy and some patients described an increased feeling of well-being. There has not been sufficient time for the authors to establish whether or not the offspring are subject to the disease but all are progressing normally. As it seems that even a hereditary factor can probably be disregarded, from every point of view there is no reason to discourage pregnancy.

Doreen Daley

10. Hiatus Hernia and Pregnancy.

By W. A. W. DUTTON and H. J. BLAND. *Brit. med. J.*, **2**, 564-566. Oct. 17, 1953. 18 refs.

Herniation of part of the stomach through the oesophageal hiatus of the diaphragm is commonly overlooked. The condition is often precipitated by a rise in intra-abdominal pressure and by recumbency and laxity of the tissues at the oesophageal ring is common.

The symptoms are protean and include epigastric discomfort, vomiting, retro-sternal pain and dysphagia due to oesophagitis and, later, there is a chance of haematemesis or stricture.

There are few recorded cases of this condition in pregnancy but the authors agree that heartburn is a constant symptom and that vomiting, with or without haematemesis, may be severe. These symptoms are aggravated by recumbency, worse in the last trimester and tend to clear up after delivery.

The authors report 9 cases seen between 1950 and 1952. Ages ranged from 23-40 years. Seven of the women were pregnant when seen and the others had both had 2 pregnancies accompanied by severe vomiting which was relieved after delivery, only to recur when they grew fatter in later years. In most of the women, severe vomiting started early in pregnancy though there was a tendency to exacerbation of the vomiting and to severe discomfort from heartburn about the 5th month. Severe vomiting in labour was a feature of many of the reports. In 6 cases there was a varying amount of haematemesis. The symptoms and radiological signs tended to clear up soon after delivery but the 23-year old patient developed severe dysphagia necessitating surgical treatment for an oesophageal stricture a few months later.

It is stressed that proof of hiatus herniation needs skilful radiology and that resolution is so rapid in the puerperium that it may then be too late for the diagnosis to be established.

Hiatus hernia does not always cause trouble in pregnancy nor is such a hernia always responsible for heartburn, vomiting or haematemesis. The authors consider that there is need for large scale investigation of the subject.

Doreen Daley

11. The Management of Postmaturity.

By D. RACKER, G. H. BURGESS and G. MANLY. *Lancet*, **2**, 953-956. Nov. 7, 1953. 4 tables. 11 refs.

The authors have recorded their observations and results in the study of pregnancies which were prolonged

past the expected date of confinement. Patients were placed into three groups. The first group consisted of patients whose labour was induced at term. If medical induction failed, surgical induction was carried out. The second group consisted of patients who were allowed to continue more than 7 days beyond the expected date of delivery to spontaneous postmature labour. The third group acted as controls and consisted of women whose pregnancy ended in spontaneous labour at term (from 7 days before to 7 days after the expected date of delivery). The stillbirth rates in the groups were 1·47 per cent, 4·63 per cent and 1·54 per cent respectively. In the postmature group, the stillbirth rate was 2·31 per cent for 7-13 days postmature labour and 8·72 per cent for 14 days or more postmature labour. The forceps rate in the induced group was less than half that in the postmature group. Caesarean section was necessary in 1 patient of the induced group and in 8 of the postmature group. Three intra-uterine deaths occurred in the postmature group. The authors conclude that it is dangerous to allow a woman to exceed her expected date of delivery more than a short period (probably 7 days) except in cases where there is serious doubt about the history.

H. H. Fouracre Barns

LABOUR

12. **Intravenous Alcohol in Obstetrical Labour.**

By H. B. Bourne, R. C. Ross and N. W. Philpott. *Canad. med. Ass. J.*, **69**, 250-253, Sept. 1953. 3 refs.

This is a survey of 100 patients in labour.

25 were sedated with 5 per cent Travenol in 5 per cent glucose.

25 were sedated with Demerol alone.

25 were sedated with Travamine Alcohol, i.e. 7½ per cent alcohol with protein hydrolysate.

25 were sedated with 5 per cent Travenol and Demerol.

Method. The Travenol was given as an initial dose of 250-300 ml. in 20 minutes and then carried on at 60-80 drops per minute. The Travamine was given as an initial dose of 150 ml. and then adjusted.

Results. Travenol alone

1. Unless 4-5 cm. dilatation was present, the solution markedly slowed labour.

2. Five out of 25 obtained good and 10 obtained fair results.

3. The effect was so variable that constant observation was necessary.

4. All babies cried spontaneously.

The average length of labour was 22 hours, 28 minutes. The average blood loss was 264 ml.

Demerol alone (100 mg. doses)

1. Two out of 25 obtained good, while 8 obtained fair results.

2. Vomiting often occurred.

3. Six babies were sleepy and one required tubbing.

The average length of labour was 19 hours, 8 minutes. The average blood loss was 332 ml.

Travamine Alcohol

1. Four out of 25 obtained good and 13 obtained fair results.

2. In sedative doses it produced very striking decrease in the strength and frequency of the uterine contractions.

3. It was difficult to control.

4. Four babies were sleepy—2 required resuscitation.

The average length of labour was 25 hours, 48 minutes.

There were 5 post-partum haemorrhages—2 over 1,000 ml., 3 over 500 ml. The average blood loss was 421 ml.

Travenol plus Demerol (50 mg. doses)

1. This was the best combination—13 obtained good and 5 obtained fair results.

2. There was very little slowing of labour. Three babies were sleepy.

The average length of labour was 19 hours, 58 minutes. The average blood loss was 352 ml.

The placenta offers no barrier to intravenous alcohol the foetal blood levels rapidly equalizing the maternal.

From these findings the authors conclude that intravenous alcohol is useful in those labours requiring both sedation and supportive therapy. They maintain it is contraindicated in inertia.

[Surely these are contradictory statements. It is obvious that intravenous alcohol, particularly in the higher concentration, achieves its sedative effect at the expense of markedly increasing the length of labour together with the post-partum haemorrhage rate. Five severe haemorrhages in 25 cases is very alarming. From this small series, the definite deduction that alcohol is a superior sedative to Demerol is surely not warranted.]

R. A. H. Kinch

LACTATION

13. **Lactation and Fluid Intake.**

By R. S. Illingworth and B. Kilpatrick. *Lancet*, **2**, 1175-1177. Dec. 5, 1953. 10 tables. 6 refs.

This is an important investigation into the effects of fluid intake on lactation. In a carefully controlled experiment, 106 mothers were left to drink only what they desired and 104 mothers were asked to drink at least 6 pints a day.

There was no significant difference in the gain in weight of the babies in the 2 groups at the age of 9 days and 1 month in relation to the birth weight. Test-feeding was carried out on the 8th day. No significant difference in the amount of milk produced was found in the 2 groups, except where the largest babies (more than 7 pounds 13 ounces) were concerned. In this particular instance more milk was produced by the mothers in the ordinary fluid intake group. No significant difference in the incidence of breast feeding on discharge from hospital and at 1 month was found in the 2 groups.

The investigation shows that the forcing of fluids in the puerperium has no beneficial effect in increasing milk production but that it may actually reduce it. The authors conclude that the practice of instructing lactating women to drink large quantities of fluid should be abandoned.

H. H. Fouracre Barns

INFANT

14. Some Aspects of Prolonged Gestation.

By G. D. Ley. *Med. J. Aust.*, **2**, 749-752. Nov. 14, 1953.

In the presence of prolonged gestation the chief problem is to determine whether labour should be induced. The investigation was undertaken to try to assess the risks which attend prolongation of gestation.

At the Women's Hospital, Melbourne, the term "post-mature" has been used only when the new-born showed dry peeling skin, excessively long finger nails, small amount of subcutaneous fat, increased length in relation to body weight. Sometimes foetal death before or during labour was included and sometimes neonatal feeding difficulties. Usually there is a reduction in the quantity of liquor amnii which is turbid, dark and thick.

Only those cases in which the period of amenorrhoea had reached or exceeded 294 days were studied. Patients with irregular or uncertain menstrual histories were excluded as were those with a cycle greater than 35 days. Of patients thus selected 643 were studied. Of these 70 were delivered after periods of amenorrhoea of 294 days or more, that is 11 per cent. It is suggested that in some women at least prolongation of pregnancy constitutes a recurrent problem.

In the post-mature group 2 babies were stillborn and there were no neonatal deaths. Post-mortem examination of these 2 stillborn babies failed to reveal a satisfactory anatomical explanation of death.

Of the patients who did not have prolonged periods of gestation 430 were delivered spontaneously with 5 still births and 4 neonatal deaths. The author found that there was a definite relation between dry peeling skin in the newborn and prolonged gestation.

Routine surgical induction of labour in post-maturity cannot be recommended owing to the low foetal mortality rate in this series and the fact that surgical induction carries a considerable risk to the foetus.

S. Devenish Meares

15. Treatment of Asphyxia Neonatorum.

By J. M. Lord, B. W. Powell and H. Roberts. *Lancet*, **2**, 1001-1004. Nov. 14, 1953. 5 tables. 15 refs.

The authors record the routine they employ for the immediate resuscitation of the asphyxiated newborn infant and their results during a period of 4 years. The method adopted consists of early aspiration of the pharynx, endotracheal insufflation for mature infants and gastric oxygen for small premature infants. Endotracheal insufflation is not recommended for small premature babies owing to the shock induced. Augmented respiration is used for persistent atelectasis. Seven per cent of the neonatal deaths were due to asphyxia.

H. H. Fouracre Barns

16. Resuscitation of the Newborn with Intragastric Oxygen (Akerren's Method).

By H. K. Waller and D. Morris. *Lancet*, **2**, 951-952. Nov. 7, 1953. 1 fig. 5 refs.

The authors record their experience of treating 48 severely asphyxiated newborn babies by means of intragastric oxygen. The oxygen is passed from cylinder through a pressure bag and a Jaques catheter into the stomach. A second Jaques catheter is passed into the stomach to act as a safety or outlet catheter. Of the 48 babies treated 7 did not respond; 41 were resuscitated but of these 3 subsequently died. Post-mortem examination showed cerebral haemorrhage in 3 babies and atelectasis and evidence of asphyxia in the remaining 7. No examination was made for the presence of hyaline membrane. In the babies responding to the treatment, the onset of breathing occurred in from 1 to 75 minutes. A miniature light-weight oxygen container is described which will enable the method to be practised in domiciliary midwifery. The authors also state that they have used the method successfully in the treatment of severe cyanotic attacks in premature infants.

H. H. Fouracre Barns

17. Icterus of the Brain in the Newborn.

By A. E. Claireaux, P. G. Cole and G. H. Lathe. *Lancet*, **2**, 1226-1230. Dec. 12, 1953. 4 figs. 18 refs.

Investigation of yellow pigmentation of the brain in newborn babies dying in the neonatal period has been carried out by the authors during 1948-52. There were 376 autopsies and of these 33 (8·8 per cent) showed brain pigmentation. Twenty-four (including one pair of twins) showed evidence of rhesus iso-immunization and the remaining 9 were all premature infants with no evidence of rhesus incompatibility. The infants with haemolytic disease seldom survived more than 4 days, whereas no infant in the premature group died before the 5th day. All the mothers of the babies with haemolytic disease were rhesus negative and had antibodies in their serum, whereas investigations of 7 of the 9 mothers of the premature babies showed that they were rhesus positive and none had antibodies in her serum.

The distribution of the brain pigmentation was variable and no distinction could be made between the two groups of cases. The pigment was extracted from the brains of 2 babies of each group and examined biochemically. The authors conclude from this examination that the pigment was identical in the two groups and was bilirubin. In addition they found that there was a bilirubin-retaining liquid in the brain. They state that the indirect-reacting pigment found in the serum and characteristic of haemolytic jaundice is bilirubin whereas the direct-reacting pigment which predominates in obstructive jaundice is not, but is particularly easily oxidized to green derivatives. They suggest that the bilirubin-retaining lipid of the brain gives it a selective attraction for bilirubin whereas the lipid has no affinity for the direct-reacting bile pigment, and thus the brain is unaffected by this type of pigment. Hence the occurrence of extreme jaundice with greatly increased quantities of bile pigments in the serum does not in itself necessarily lead to pigmentation of the neonatal brain provided that the pigment in the form of bilirubin is relatively small. The authors make the point that conversion of bilirubin (by the liver) to the direct-reacting pigment tends to protect the neonatal brain

from icterus. They suggest that a defect in this conversion may be the primary factor leading to the brain icterus of premature babies in whom no increased production of bilirubin has yet been demonstrated, and maintain that this is consistent with the longer survival of the premature baby than of the one affected with haemolytic disease.

H. H. Fouracre Barns

18. **The Incidence of Congenital Malformations following Maternal Rubella at Various Stages of Pregnancy.**

By I. S. COLLINS. *Med. J. Aust.*, **2**, 456-458. Sept. 19, 1953. 19 refs.

Having reviewed the literature, the author concludes that where the mother contracts rubella during the first 4 months of pregnancy there is a 70-80 per cent chance of malformation in the offspring. If rubella is contracted after the fourth month the risk of malformation of the foetus is not very great.

S. Devenish Meares

19. **Intracerebral and Meningeal Haemorrhages in Perinatally Deceased Infants.**

By O. GRÖNTOFT. *Acta obstet. gynec. scand.*, **32**, 308-334 and 458-498. 1953. 30 figs. 81 refs.

This is a study of necropsy material, comprising 319 neonatal deaths. In 36·7 per cent of these cases, which were investigated at the Institute of Pathological Anatomy of Gothenburg, Sweden, macroscopically visible haemorrhages were present. From the wealth of clinical and patho-anatomical details presented in this paper the following results stand out clearly.

The haemorrhages fell into 2 groups, namely (1) intracerebral haemorrhages (from the terminal vein, from the choroid plexus, or in the cerebral parenchyma) and (2) meningeal haemorrhages (lacerations of the tentorium cerebelli with slight or severe haemorrhage, tentorial laceration with bleeding occurring after foetal death, convexity haemorrhage of the cerebrum, minor vascular ruptures, isolated haemorrhage in the pia mater).

Two factors predominated aetiologically, namely (1) asphyxia and (2) birth trauma. Terminal vein haemorrhage, which was found in premature infants only, may occur in cases of intra-uterine death before the onset of labour, during labour, or after delivery; this type of bleeding is accompanied by signs of asphyxia, both clinical and anatomical. It is assumed that terminal vein haemorrhage arises as the result of venous congestion during an attack of asphyxia. The latter condition also plays a decisive role in cases of haemorrhage in the cerebral parenchyma and of isolated bleeding in the pia mater.

Most cases of intracranial haemorrhage caused by birth trauma take place from tentorial lacerations. These injuries occur with increasing frequency the larger the infant is—in contrast to asphyxial haemorrhage which occurs with increasing frequency the smaller the infant. Tentorial lacerations with resultant intracranial haemorrhage can also arise during the delivery of a dead infant.

The importance of vitamin K in intracranial bleeding in newborn infants is clearly demonstrated by convexity haemorrhages of the cerebrum. This type of bleeding occurred in 15-20 per cent of cases not treated with vitamin K, whereas no such haemorrhage was observed, nor has been reported in the literature, in cases treated with this vitamin. In other groups of intracranial haemorrhage the importance of vitamin K appears to be small.

[This is a most painstaking and clear presentation of the problem of intracranial haemorrhage, richly illustrated by tables, figures and references to the literature. It is well worth reading in its entirety.]

N. Alders

20. **Erythroblastosis Caused by Rh-Incompatible Blood Transfusion.**

By O. HARTMAN and O. J. BRENDEMOEN. *Acta obstet. gynec. scand.*, **32**, 444-451. 1953. 7 figs. 1 ref.

Working at the Institute of Public Health in Oslo, the authors have been able to collect information on the subsequent history of 60 out of 63 Rh (D) negative women who had been immunized by blood-transfusion. These 60 women gave birth to 79 children (including one pair of twins) after transfusion. Of these 79 children 16 were stillborn and 13 died very soon—mostly during the first few days—after birth. The severity of erythroblastosis was strongly correlated to the albumen anti-D titre in the mother's blood. Forty-four children of type D positive or of unknown D type, and 6 children known to be D negative survived. Thus the death-rate of children born to D negative women subsequent to immunization was 37 per cent in spite of the fact that the majority of those requiring treatment were transfused. As 6 of the children were shown to be D negative, and as some of the children of unknown D type were probably also D negative, the mortality of D positive children born to these 60 mothers most probably exceeded 40 per cent.

The importance of Rh typing before transfusion is stressed.

N. Alders

OBSTETRIC OPERATIONS

21. **The Place of Forceps in Present-day Obstetrics.**

By T. N. A. JEFFCOATE. *Brit. med. J.*, **2**, 951-955. Oct. 31, 1953. 5 figs. 11 refs.

Opening a discussion on forceps delivery at the Annual Meeting of the British Medical Association, the author gave a brief historical résumé and then developed his theme of the revolution in obstetrical methods and outlook in the past 25 years which has been responsible for a dramatic fall in mortality and morbidity rates for both mother and infant.

At the Liverpool Maternity Hospital, the neo-natal death rate fell by one-third and the stillbirth rate by two-thirds in the years 1926-50, while 50,622 deliveries were conducted at the hospital. Birth injury, which has long been credited with about 33 per cent of the deaths, now accounts for only 10 per cent. During this time the forceps delivery rate rose from 6-7 per cent to 16-17 per cent and the Caesarean section rate from 5 per cent to

15 per cent. At the same time, the foetal mortality from forceps delivery fell from 20 to 2 per cent and only one mother has died as a direct result of the operation in the past 15 years. Particularly important factors responsible for these improved results are the increasing emphasis on accurate cephalic application of the blades and timing the operation before the foetus becomes distressed from asphyxia. In general, nowadays, babies previously born dead after forceps extraction are delivered alive by Caesarean section and those that were stillborn after spontaneous delivery are now delivered alive by forceps.

The indications for forceps delivery should be related to the available obstetrical skill and environmental facilities. In domiciliary practice, a "prophylactic" operation is inadvisable and forceps delivery should be restricted to those cases where there is an indication to expedite delivery and the head is really well down in the pelvis and visible at the vulva. In hospital, low forceps application with episiotomy carries less risk than a prolonged second stage; rotation is unnecessary and outlet contraction very rare if the rest of the pelvis is adequate.

Mid-forceps delivery is quite another problem, and merits an experienced obstetrician and hospital surroundings. Rotation is often needed and mid-plane disproportion may not have been recognized, so that unexpected difficulties may arise, particularly perhaps in the multipara with an unusually large baby. In such circumstances, continued efforts to achieve vaginal delivery can only result in stillbirth and maternal trauma and the author supports the view that there is a place for "trial of forceps" on occasion. Cavity disproportion is assessed in this way, just as trial of labour tests brim disproportion and in either case delivery can be effected by Caesarean section if the trial should fail.

In discussing whether forceps blades protect the foetal head, the author feels that this has been established in the special case of the after-coming head but he is less dogmatic regarding the fore-coming head in premature labour.

Properly applied forceps should do no harm to the mother and their well-timed application may help to prevent prolapse. In any case, mental and physical stress is reduced if labour is shortened. The main risk to the mother is, however, not the operation but the anaesthetic and there were 6 anaesthetic deaths in the series reviewed during the 15 years prior to 1950. Inhalation pneumonia continues to occur, especially after prolonged labour and inhalation anaesthesia also increases third stage complications. Constant recognition of these risks reduces them to a minimum but they cannot be entirely prevented and they constitute the chief reasons for advocating local analgesia for low forceps operations.

Doreen Daley

22. "Failed Forceps": A Review of 37 Cases.

By R. G. LAW. *Brit. med. J.*, **2**, 955-957. Oct. 31, 1953. 5 figs. 9 refs.

The author has reviewed 37 cases of failed forceps deliveries admitted to the Norfolk and Norwich Hospital between 1st January, 1948 and 31st May, 1952. Twenty-one were primigravidae, 16 multiparae.

The total foetal loss was 24·3 per cent, including one case of hydrocephalus. No mother died, but the maternal morbidity rate was 27·0 per cent. Labour tended to be prolonged and lasted over 24 hours in 63·2 per cent of cases.

The previous obstetric history in the multiparae showed previous dystocia in 50 per cent in the 11 cases in which the weight of the former infant was known. In 7 the present infant was larger than its forerunners.

The causes of failure to deliver were disproportion in 7 (18·9 per cent). Incompletely dilated cervix was a main factor in 6 and a subsidiary factor in a further 7. Malposition of the head was a main factor in 18 and a subsidiary factor in 6.

An analysis of the method of delivery in hospital showed that in 35·1 per cent delivery was ultimately spontaneous, or by an easy low forceps. Craniotomy was necessary in 2 cases, including the hydrocephalic foetus. Abdominal delivery was necessary in 6.

The author drew the conclusion that disproportion was rarely the cause of dystocia in the primigravidae but the most common cause in the multiparae, when it should have been detected prior to labour. Deliberate delivery through an incompletely dilated os is fraught with danger, seldom necessary and should only be attempted by the experienced obstetrician in hospital. Accurate determination of the position of the foetal head is also essential before forceps delivery is attempted.

Eileen D. M. Wilson

23. Caesarean Section in Elderly Primigravidae.

By L. HIRVONEN and K. NIEMINEVA. *Ann. chir. gynec. fenn.*, **42**, 7-62. 1953. 2 figs. 48 refs.

This is a very full study of 1,000 sections on elderly primiparae performed in Helsinki between 1907 and 1950. Any case of over 30 years of age is taken to be an elderly primipara. Prior to 1946 there had been 423 sections in elderly primiparae whereas from 1946 to 1950 there were 577 sections. This increase is due to a widening of the indications for section rather than an increase in the number of absolute indications. Uterine inertia, foetal asphyxia, long-wanted child and rigidity of the soft parts are specially important indications. Among the foetal indications it was noted that 28·6 per cent had been married more than 6 years prior to conception. The Caesarean rate among elderly primiparae between 1946 and 1950 was 19·4 per cent compared with a general section rate for all cases of 5·8 per cent. The corrected maternal rate for the whole series was 2·1 per cent but in 1946-50 it was only 0·7 per cent. The uncorrected foetal mortality was 4·8 per cent, the corrected being 2·0 per cent. Labour prior to section did not affect the foetal mortality rate but raised the maternal mortality rate. The length of time of rupture of membranes prior to section had no adverse effect on either mother or child. Over the whole series the number of sections done annually for contracted pelvis has decreased and correspondingly the average pelvic measurements have increased. Section for breech presentation has increased especially in the 30-34 age group. The author

lays great stress on the importance of Caesarean section as a means of delivery in the elderly primipara.

D. M. Sheppard

24. **Vaginal Delivery following Caesarean Section.** By J. NATTRASS. *Med. J. Aust.*, **2**, 329-332. Aug. 29, 1953. 1 ref.

This is a review from 1948 to 1951 inclusive from the Women's Hospital, Melbourne, of the 106 records of patients who had previously been delivered by Caesarean section and in whom elective repetition of this operation was not performed.

During these 4 years 23,497 mothers were delivered at the Hospital. Of the 106 cases, in 19 the attempt at vaginal delivery was unsuccessful and Caesarean section was repeated. During the same period, 173 elective "repeat" Caesarean sections were done.

There were no maternal deaths among those delivered vaginally and there was 1 maternal death among the patients subjected to elective "repeat" operations.

Twenty-two of the previous Caesarean sections had been of the classical type. In 2 patients the uterus ruptured. There were 6 still-births and 2 neonatal deaths.

The author concludes that the majority of patients are capable of giving birth to one or more babies *per vias naturales* subsequent to a Caesarean section though a few will suffer rupture of the uterus even in those cases in which, from the history, one would expect the scar to be strong.

Where the indication for the previous Caesarean section had been of a transient type, where the incision had been in the lower uterine segment, where it is known that a satisfactory technique was employed, where the puerperium had been uneventful, and where the facilities of a fully equipped hospital are available, vaginal delivery should be attempted.

S. Devenish Meares

25. **The Perinatal Mortality in Caesarean Section.** By K. SOIVA. *Acta obstet. gynec. scand.*, **32**, 422-432. 7 figs. 33 refs.

The author has collected 925 cases of abdominal Caesarean section, which were performed at the Helsinki Institute of Obstetrics between 1945 and 1951. Only cases in which the infant's weight was at least 600 g. were included. All the infants who died before or during delivery or within 14 days of delivery (a total of 56, i.e. 6·1 per cent) have been included as cases of "perinatal mortality".

The methods and results of deliveries in the period 1934 to 1944 were compared with those occurring between 1945 and 1951. While the results in general have improved (the maternal mortality dropped from 0·26 to 0·07 per cent, and the uncorrected foetal mortality from 3·5 to 2·0 per cent), and while the maternal prognosis in Caesarean section (the incidence of which rose from 2·33 to 4·22 per cent) has been reduced from 3·5 to 1·0 per cent, the foetal death-rate in Caesarean section has remained approximately unchanged (about 6 per cent). In the author's material deaths among infants born by Caesarean section are 3 times as numerous as in deliveries in general.

Analysis of the causes of perinatal mortality in Caesarean section in the period 1945 to 1951 revealed that 31 of the 56 infants that were lost were premature. A total of 68 premature infants were born by Caesarean section in this period. This means that, if Caesarean section is performed whilst the foetus is premature, one must be prepared for a foetal loss of almost 50 per cent. Twenty-five of the full-time Caesarean section infants died (necropsy was carried out in one-third of these cases). There were 5 cases of malformation incompatible with life, 2 instances of fatal neonatal infection, 15 cases of asphyxia leading to death either during or a few hours after delivery, and 3 cases of intracranial haemorrhage.

It is concluded that, if the foetus is premature, operation should be postponed as long as possible, e.g., by conservative treatment of toxaemias of late pregnancy and of placenta praevia; monsters should be diagnosed before operation; Caesarean section should be performed before the foetus is irreparably damaged by toxaemia or asphyxia; the anaesthetic should be of a type having the least effect on the foetus; the infant must be handled with care during the operation; special attention must be paid to the post-natal care of the infant.

N. Alders

GYNAECOLOGY

26. **An Investigation into the Liver Threshold for Oestrogens in Rats and Guinea Pigs.** (Versuche zur Ermittlung der Leberschwellenwertes für östrogene Stoffe bei Ratten und Meerschweinchen.) By A. LÉVY. *Gynaecologia, Basle*, **136**, 222-242. Oct. 1953. 5 figs. 53 refs.

An attempt was made to determine if the liver has a threshold for oestrogenic substances. Tablets of oestradiol and oestradiol benzoate were implanted in decreasing doses into the spleen of castrated rats and guinea pigs.

It was found that long continued application of 3 to 4 gamma per day either into the spleen or subcutaneously caused intense hormonal effect. One gamma per day had little effect. It is concluded that there is no evidence that the liver is capable of inactivating oestrogenic hormones given in excessive doses or over a prolonged period.

Comment. The question of the metabolism of the sex hormones still remains obscure and difficult and this study presents mainly negative evidence.

Josephine Barnes

27. **The Excretion of Corticoids in Healthy Women.** (Die Corticoidausscheidung gesunder Frauen.) By H. J. STAEMMLER. *Arch. Gynäk.*, **182**, 506-520. 1953. 4 figs. 1 table. 102 refs.

The author has estimated the excretion of corticoid hormones in 5 healthy women with regular menstruation over a total of 11 cycles. Estimations were carried out every other day for one week premenstrually and during the menstrual flow, otherwise on every 4th day. The average daily excretion was 880 γ with a scatter of $\pm$25 per cent. The ratio between the minero- and glucocorticoids was 1/1·63. The intermenstrual period

was characterized by a relatively constant excretion of 800 γ. There was a steady increase of excretion during the secretory phase with a peak excretion value of 1,145 γ on the 25th day; this was followed by a sharp fall below the average excretory level of the intermenstrual phase on the 26th and 27th day of the cycle with a subsequent rise to 1,000 γ on the 28th day. Corticoid excretion during menstruation showed great individual variations, but there was, on the whole, a tendency to fall.

In women with genital hypoplasia these values were reduced to almost half.

Twenty-nine pregnant women were also studied, of whom 148 urines were examined. Three distinct phases could be distinguished. Up to the 4th month of gestation corticoid excretion averaged 942 γ, thus equalling the menstrual phase. Between the 5th and 6th month there was a significant decrease in excretion to 550 γ, which was followed by a marked rise to 995 γ from the 7th month to the end of term. The puerperium was characterized by a sharp fall in corticoid excretion.

Forty-one urines from 14 menopausal women were also examined. Average excretion values were about 520 γ per day, i.e., 40 per cent less than in young women.

E. Wachtel

28. **Primary Amenorrhoea.** (Die primäre Amenorrhoe.)
By E. PHILIPP. *Arch. Gynäk.*, **183**, 247-264. 1953. 13 figs. 1 table. 3 refs.

The author subdivides primary amenorrhoea into 4 aetiological groups, viz., uterine, ovarian, pituitary and hypothalamic amenorrhoea.

Uterine amenorrhoea occurs in 2 varieties, one comprising cases with an anatomically normal organ and the other characterized by uterine developmental arrest. The endometrium in both these groups is poorly developed, but the oestrogen level, as judged by vaginal smears, appears to be adequate. No oestrogen nor progesterone withdrawal bleeding can be produced. These patients have a female appearance and hormonal excretory values are normal. Endocrine treatment has no effect. These cases are rare.

Primary ovarian amenorrhoea occurs more often and is seen in two forms, ovarian agenesis and ovarian hypoplasia. The former is diagnosed by the characteristic syndrome of amenorrhoea, absence of all secondary sexual characteristics, dwarfism, infantilism, delayed epiphyseal closure, presence of a hypoplastic uterus and endometrium which can be stimulated by oestrogen therapy. Withdrawal bleeding can be induced with oestrogens, but fails to occur after progesterone. Urinary gonadotrophins are high.

In ovarian hypoplasia the ovaries may be of normal size or enlarged, but they show a decrease in the number of follicles and no corpora lutea. The uterus is small, the endometrium poorly developed and non-functioning. Secondary sex characteristics are normal, hormonal excretion is variable, there is no or only slight delay in epiphyseal closure. Oestrogen and progesterone withdrawal bleedings can be induced.

Pituitary primary amenorrhoea is characterized by low or absent gonadotrophin production, the lack of FSH being recognizable by a negative pregnandiol test. Oestrogen withdrawal bleeding occurs.

Hypothalamic primary amenorrhoea is at present a vague concept and further research will be necessary to establish whether it presents an endocrine entity.

E. Wachtel

29. **Yeasts in the Vaginal Flora: their Incidence and Importance.**
By S. M. DAWKINS, J. M. B. EDWARDS and R. W. RIDDELL. *Lancet*, **2**, 1230-1233. Dec. 12, 1953. 6 tables. 16 refs.

The authors have investigated the incidence of yeast-like fungi in the vagina of 500 patients attending family planning clinics. All patients had vulval and vaginal swabs taken, from which cultures were inoculated and smears prepared. Aspirates from a vaginal pool (using 1 ml. of sterile 0·85 per cent saline) were also examined for *Trichomonas vaginalis*.

Yeast-like fungi were cultured from 57 patients. *Candida albicans* was found in 38 of these, but only 6 patients had recognizable vaginal thrush.

Various species of yeast were indistinguishable in smear preparations and such preparations were found to be useless as a guide to the presence of *C. albicans*. Only about two-thirds of the patients harbouring *C. albicans* show the presence of yeasts in smears. Close associations were found between the presence of *C. albicans* on the one hand, and vulvo-vaginitis, discharge and severe pruritus on the other. The incidence of *C. albicans* was also higher in those women who douched regularly. However, 14 of the 38 patients harbouring *C. albicans* had neither signs nor symptoms and the authors stress the danger that in such cases the gynaecologist will not take the precautions he would take if he were dealing with a case of obvious vaginal thrush. The hazard of transferring the organism from one patient to another in a gynaecological clinic clearly exists unless adequate aseptic techniques are observed.

H. H. Fouracre Barns

30. **Granulosa Cell Tumour of the Ovary with Spread to the Endometrium and Cervix.**
By A. R. H. DUGGAN. *Med. J. Aust.*, **2**, 99-100. July 18, 1953. 3 figs.

The patient was a widow who had never been pregnant. From the age of 29 to 43 her periods were scanty with intervals of several months of amenorrhoea. For some months there had been evidence of slight bleeding and for 3 weeks continuous and at times excessive loss. There was no pain, the uterus was not enlarged, mobility was a little restricted and there was tenderness on the right side.

A small polypus was observed at the external cervical os. The right appendages were normal and the left ovary was the size of a golf ball, firm and not tender. At operation on dilating the cervix small pieces of friable tissue came away. Curettage removed large quantities of this material. It was considered that there was an adenocarcinoma of the uterus with metastases in the left ovary.

On attempting to lift the left ovary from the abdomen it broke into irregular fragments.

A nodule half an inch in diameter was found on the right side of the uterus under the upper edge of the bladder. The right ovary was normal. Total hysterectomy and bilateral salpingo-oöphorectomy was done. A large fungating friable mass filled the cavity of the uterus. Microscopically there was cystic glandular hyperplasia of the uterus invaded by typical follicular type granulosa cell carcinoma. There were granulosa cell deposits in the myometrium and cervical tissue together with granulosa cell carcinoma in the left ovary and the uterine nodule.

S. Devenish Meares

31. **Sertoli Cell Tumours of the Ovary.** (Androblastoma tubulare lipoides Teilum.)

By C. v. NUMRES and T. GYLLING. *Ann. chir. gynec. fenn.*, **42**, 161-167. 1953. 5 figs. 8 refs.

The authors, reviewing cases diagnosed as granulosa cell tumours discovered 3 cases where the microscopic appearance and clinical history necessitated reclassification of these cases as Sertoli cell tumours, i.e., feminizing testicular-like tumours occurring in the ovary. The 3 cases were all about the menopause and characterized by irregular bleeding and the finding of cystic glandular hyperplasia of the endometrium at curettage.

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